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ATTORNEY DOCKET NO.: AM100212 CON (WYNC-0331) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Megan Tran and Gary P. Stack **Confirmation No.: 8285**

Application No.: 10/661,182 **Group Art Unit: 1625**

Filing Date: September 12, 2003 **Examiner: Huang, Evelyn Mei**

For: Antidepressant Azaheterocyclymethyl Derivatives of 1,4-Dioxino[2,3-B]Pyridine

EXPRESS MAIL LABEL NO: EV 325726295 US
DATE OF DEPOSIT: April 14, 2005

EV325726295US

MS Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF TRANSMITTAL PURSUANT TO 37 CFR § 41.37

Transmitted herewith is the APPEAL BRIEF in this application with respect to the Notice of Appeal received by The United States Patent and Trademark Office on **February 16, 2005**.

☐ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27 .

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:

☐ an Independent Inventor

☐ a Small Business Concern

☐ a Nonprofit Organization.

☐ Petition is hereby made under 37 CFR § 1.136(a) (fees: 37 CFR § 1.17(a)(1)-(4) to extend the time for response to the Office Action of to and through comprising an extension of the shortened statutory period of month(s).

04/19/2005 EFLORES 00000015 10661182
01 FC:1402 500.00 OP

DOCKET NO.: AM100212 CON (WYNC-0331) **PATENT**

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
☒ APPEAL BRIEF FEE	$250	$	$500	$500.00
☐ ONE MONTH EXTENSION OF TIME	$60	$	$120	$0
☐ TWO MONTH EXTENSION OF TIME	$225	$	$450	$0
☐ THREE MONTH EXTENSION OF TIME	$510	$	$1020	$0
☐ FOUR MONTH EXTENSION OF TIME	$795	$	$1590	$0
☐ FIVE MONTH EXTENSION OF TIME	$1080	$	$2160	$0
☐ LESS ANY EXTENSION FEE ALREADY PAID	minus	($)	minus	($0)
TOTAL FEE DUE		$0		$500.00

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.

☒ A check in the amount of **$500.00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

☐ Please charge Deposit Account No. 23-3050 in the amount of **$ .00**. This sheet is attached in duplicate.

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

Date: April 14, 2005

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the rejections of claims 19 to 33 dated September 20, 2004. A Notice of Appeal was filed on February 16, 2005.

1. REAL PARTY IN INTEREST

Based on information supplied by Appellant and to the best of the undersigned's knowledge, the real party in interest in the above-identified patent application is Wyeth.

2. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

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3. STATUS OF CLAIMS

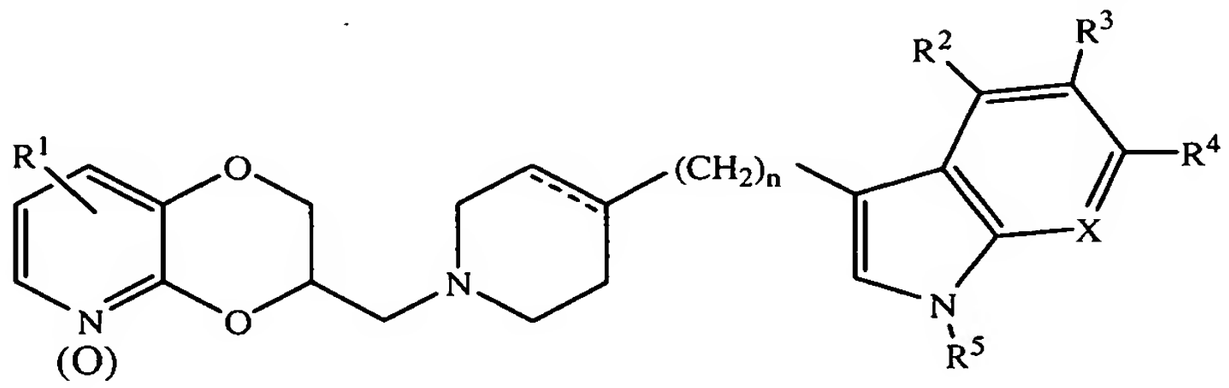
Claims 1 to 18 are cancelled. Claim 19 to 33 are pending and rejected. There are no claims that are allowed, withdrawn, or objected to.

4. STATUS OF AMENDMENTS

The Amendment after Final Rejection, filed December 17, 2004, was entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 19 to 33, as set forth in the Claims Appendix, are directed a method of treating a subject suffering from obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation, comprising the step of providing to said subject suffering from said condition a therapeutically effective amount of a compound of formula I:



I

(page 2, line 10 to page 3, line 31).

The compounds of formula I are dual selective serotonin reuptake inhibitors (SSRI)/5-HT_{1A} serotonin receptor antagonists (page 9, line 4 to page 10, line 33) Compounds that combine the SSRI and $5HT_{1A}$ antagonist activity, like those of the present invention, permit a modified physiological serotonin uptake cycle wherein serotonin uptake is inhibited, thereby effecting increased amounts of synaptic serotonin. The $5HT_{1A}$ activity of the compounds of formula I contemporaneously block presynaptic serotonin receptors and thus prevent feedback inhibition from delaying synaptic serotonin increase. This decreases the SSRI latency period that leads so many patients erroneously to believe that their treatment has been

unsuccessful. Accordingly, the compounds of formula I are expected to useful in the treatment of conditions responsive to serotonin reuptake inhibition, specifically including obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation, especially since they do not suffer from latent efficacy (page 10, lines 23 to 33).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 19 to 33 are rejected as allegedly nonenabled under 35 U.S.C. § 112, first paragraph.

7. ARGUMENTS

a. ***It is has not been prima facie established that claims 19 and 21 to 33 are not enabled under 35 U.S.C. § 112, first paragraph***

In order to establish a *prima facie* case of non-enablement, the following must be established by the Patent Office:

1. a rational basis as to
   a. why the disclosure does not teach; or
   b. why to doubt the objective truth of the statements in the disclosure that purport to teach;
2. the manner and process of making and using the invention
3. that correspond in scope to the claimed invention
4. to one of ordinary skill in the pertinent technology,
5. without undue experimentation, and
6. dealing with subject matter that would not already be known to the skilled person as of the filing date of the application.

Any rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, must include evidence supporting each of these elements. Appellants respectfully submit that the Office has failed to meet its burden of establishing a *prima facie* case of non-enablement.

It has been consistently held that the first paragraph of 35 U.S.C. § 112 requires nothing more than *objective* enablement. Furthermore, a specification that teaches how to make and use the invention in terms which correspond in scope to the claims *must* be taken as complying with the firs paragraph of 35 U.S.C. § 112, *unless* there is reason to doubt the objective truth of the statements relied upon therein for enabling support. *Stahelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (B.P.A.I. 1992) (citing *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (C.C.P.A. 1971). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to ... back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

Appellants have appealed the enablement rejection because they believe that claims 19 and 21 to 33 are enabled under 35 U.S.C. § 112, first paragraph, and that, contrary to the Office's position there is an established nexus between the use of SSRI and 5-HT_{1A} receptor antagonists and the treatment of obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation. Furthermore, it is not illogical or inconsistent for the compounds of formula I to be useful in methods of treating conditions that encompass seemingly opposite characteristics. Moreover, appellants have provided representative examples to establish that the compounds of formula I are both SSRI and 5-HT_{1A} receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art.

The Office is challenging the objective truth of the use of the compounds to treat the various conditions, and, in particular, the nexus between 5-HT_{1A} receptor ligands and the treatment of obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation. The nexus between the use of SSRI and 5-HT_{1A} receptor antagonists and the treatment of obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation is recognized in the art. For example:

- US-B-6,169,098 shows that 5-HT_{1A} receptor antagonists are useful in the treatment of eating disorders (obesity, anorexia nervosa, bulimia nervosa), sexual disturbances, alcoholism, and thermoregulatory disorders (column 4, lines 24 to 32);

- Lee, *et al.*, *Formulary* 2002; 37: 312-319 shows the use of SSRIs in the treatment of alcohol dependence; eating disorders including bulimia nervosa, anorexia nervosa, and binge-eating disorders; and sexual dysfunction;
- Stone, *et al.*, *Am. Fam. Physician* 2003; 68: 498-504 describes use in the treatment of premature ejaculation;
- WO 00/34263 describes the use of antagonists of $5HT_{1A}$ receptor antagonists, *inter alia*, in the treatment of alcohol abuse;
- Sertraline, fluoxetine (*e.g.*, Prozac®), and other SSRIs have been shown to have a broad range of efficacy in the treatment of alcoholism (*see* Brady K. T., *et al.*, "Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence," *J. Clin. Psychiatry* (**1995**) 56, 502-5; Janiri L., *et al.* "Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics," *Int. Clin. Psychopharmacol.* (**1996**) 11,109-17;
- Boyer, W. F., "*Potential indications for the selective serotonin reuptake inhibitors*," *Int. Clin. Psychopharmacol.*, (**1992**) 5, 5-12 demonstrates that the common SSRI side effect of decreased appetite and subsequent weight loss appears to be most pronounced in obese patients and may be a useful effect as an adjunct to diet and exercise in cases of severe obesity; Boyer also reports that fluoxetine is an effective treatment for anorexia nervosa; fluoxetine (*e.g.*, Prozac®) is also indicated for treatment of bulimia nervosa (*see* Prozac® package insert, page 8).
- Venlafaxine (*e.g.*, Effexor®), paroxetine (*e.g.*, Paxil®), sertraline (*e.g.*, Zoloft®), and fluoxetine (*e.g.*, Prozac®) have all been shown effective in treatment of vasomotor flushing (*see, e.g.*, Stearns *et al.*, "Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial," *JAMA*, (**2003**) 289(21), 2827-34; *see also* Loprinzi, C. L. *et al.*, "Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial," *Lancet*. (**2000**) 356(9247), 2059-63);
- Paroxetine and other SSRIs have been used effectively to treat premature ejaculation (Waldinger MD, Olivier B. "*Utility of selective serotonin reuptake inhibitors in premature ejaculation.*" *Curr. Opin. Investig. Drugs.* (**2004**) 5(7), 743-7);
- It is also well-documented that reduction of negative feedback and augmentation of the serotonin reuptake mechanism can be effected by coadministration of $5HT_{1A}$

antagonists. *See* Perez V., *et al.*, "Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment," *Lancet* (**1997**) 349(9065), 1594-7; *see also* Perez V., *et al.*, "Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors," *J. Clin. Psychopharmacol.* (**2001**) 21(1), 36-45.

Each of these documents or its abstract is included in the Evidence Appendix.

Appellants have provided procedures for the assay to determine the affinity for the 5-HT transporter, the assay for the 5-HT_{1A} receptor, and the assay for the antagonist activity at 5-HT_{1A} receptor of the compounds useful in the methods of the invention in the specification on page 9, line 19 to page 10, line 11. Appellants have also provided data on page 10, lines 13 to 24 to show that representative compounds of the invention are combined serotonin reuptake inhibitors (SSRI) and 5-HT_{1A} antagonists. As such, they are useful for the treatment of diseases commonly treated with the *administration of SSRI antidepressants*, including obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation.

Appellants submit that the skilled artisan would accept the disclosed model as reasonably correlating to the claimed effects and, as such, the Office must consider accept the object truth of the information unless there is evidence in the record to the contrary. *See In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (reversing the decision that *in vitro* data did not support *in vivo* applications); Manual of Patent Examining Procedure § 2164.02.

A lack of working examples with respect to methods of treating obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation does not automatically make a patent non-enabling. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984). Additionally, 35 U.S.C. § 112 does not demand a "working example," and an application cannot be fatally defective merely because it lacks one. *In re Long*, 151 U.S.P.Q. 640 (C.C.P.A. 1966); *In re Honn et al.*, 150 U.S.P.Q. 652 (C.C.P.A. 1966); *In re Bartholome et al.*, 156 U.S.P.Q. 20 (C.C.P.A. 1967); and *Ex parte Kenega*, 189 U.S.P.Q. 62 (Pat. Off. Bd. App. 1974).

It is not the absence or presence of a structural relationship between known SSRIs and the compounds of the present invention that induces appellants to extrapolate the results of the known modulators of SSRI activity as forms of treatment for various medical conditions to the inventive compounds, but rather the *functional* relationship *viz.*, SSRI activity as demonstrated through reliable testing for serotonin uptake inhibition, that permits Appellants to provide compounds that utilize the nexus between the modulation of serotonin uptake and the treatment of certain serotonin-effected medical conditions.

Accordingly, appellants submit that they have presented representative examples that establish that the compounds of formula I are 5-HT_{1A} receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art.

Furthermore, the Office presents an oversimplified view of the etiological bases for such disorders as hyperphagia/hypophagia, alcohol dependence/cocaine addiction, and other seemingly "opposing and conflicting conditions," Final Rejection mailed September 20, 2004. As presented above, the literature reports that SSRI/5HT_{1A} antagonist combination therapy represents an effective treatment regime for each of these disorders, a fact which impugns the contention that it is impossible to treat seemingly "opposing" conditions via a single therapy regimen.

Because there is a nexus between compounds having serotonin reuptake inhibitory (SSRI) and 5-HT_{1A} antagonist activity and methods of treating obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation and because appellants have established that representative compounds exhibit this dual activity, appellants respectfully submit that there is not a reasonable basis for rejecting the claims. Accordingly, it has not been established that claims 19 and 21 to 37 are not enabled under 35 U.S.C. § 112, first paragraph.

b. ***It is has not been prima facie established that claim 20 is not enabled under 35 U.S.C. § 112, first paragraph***

Appellants have appealed the enablement rejection because they believe that claim 20 is enabled under 35 U.S.C. § 112, first paragraph, and that, contrary to the Office's position there is an established nexus between the use of SSRI and 5-HT_{1A} receptor antagonists and the treatment of anorexia nervosa and bulimia nervosa, as discussed more fully above. Furthermore, appellants have provided representative examples to establish that the compounds of formula I are both SSRI and 5-HT_{1A} receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art, as discussed more fully above. Accordingly, it has not been established that claim 20 is not enabled under 35 U.S.C. § 112, first paragraph.

8. CONCLUSION

For the foregoing reasons, it is respectfully submitted that the Office has not met its burden of establishing that claims 19 to 33 are not enabled under 35 U.S.C. § 112, first paragraph. Appellants, therefore, request that this patent application be remanded to the Patent Office with an instruction to both withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph, and allow the appealed claims.

Date: ***April 14, 2005***

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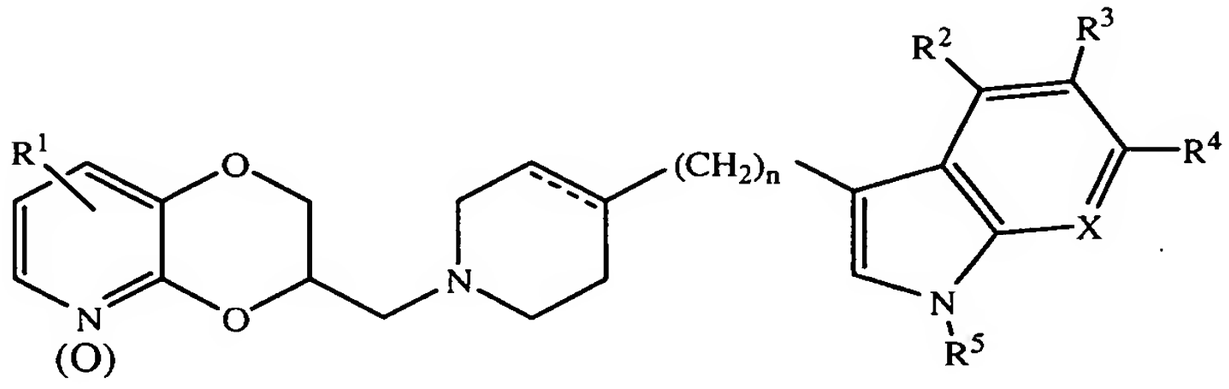
CLAIMS APPENDIX

19. A method of treating a subject suffering from a condition selected from obesity, anorexia nervosa, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation, comprising the step of:

providing to said subject suffering from said condition a therapeutically effective amount of a compound of formula I:



I

wherein

R^1 is selected from hydrogen, hydroxy, halo, cyano, carboxamide, carboalkoxy of 2 to 6 carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

R^2, R^3, R^4, and R^6 are independently selected from hydrogen, halo, cyano, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, and alkanoyloxy of 2 to 6 carbon atoms;

R^5 is hydrogen or alkyl of 1 to 6 carbon atoms;

X is CR^6 or N;

a dotted line represents an optional double bond;

(O) represents optional oxidation; and

n is an integer 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

20. A method according to claim 19, wherein said eating disorder is anorexia nervosa or bulimia nervosa.

21. A method according to claim 19, wherein said subject is a human.

22. A method according to claim 19, wherein R^1 is hydrogen.

23. A method according to claim 19, wherein R^2, R^3, and R^4 are independently selected from hydrogen, halogen, and cyano.

24. A method according to claim 19, wherein R^5 is hydrogen or lower alkyl.

25. A method according to claim 19, wherein X is CR^6.

26. A method according to claim 19, wherein R^6 is hydrogen, halo, or cyano.

27. A method according to claim 19, wherein

R^1 is attached to the 6-position of the 1,4-dioxino[2,3-b]pyridine and is hydrogen, hydroxy, halo, cyano, trifluoromethyl, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms;

R^2, R^3, and R^4 are independently selected from hydrogen, halo, cyano, alkyl of 1 to 6 carbon atoms, and alkoxy of 1 to 6 carbon atoms;

n is the integer 0 or 1; or

a pharmaceutically acceptable salt thereof.

28. A method according to claim 27, wherein

R^6 is hydrogen, halo, or cyano.

29. A method according to claim 19, wherein

R^1 is attached to the 6-position of the 1,4-dioxino[2,3-b]pyridine and is hydrogen, hydroxy or alkoxy of 1 to 6 carbon atoms;

R^2, R^3, and R^4 are independently selected from hydrogen, halo, and cyano;

R^5 is hydrogen;

X is CR^6;

N is 0; and

the dotted line represents a double bond; or

a pharmaceutically acceptable salt thereof.

30. A method according to claim 19, wherein said compound is 3-{[4-(1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl}-2,3-dihydro[1,4]dioxino[2,3-b]pyridine or a pharmaceutically acceptable salt thereof.

31. A method according to claim 19, wherein said compound is 3-{[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl}-2,3-dihydro[1,4]dioxino[2,3-b]pyridine or a pharmaceutically acceptable salt thereof.

32. A method according to claim 19, wherein said compound is 3-{1-[2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-ylmethyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1H-indole-5-carbonitrile or a pharmaceutically acceptable salt thereof.

33. A method according to claim 19, wherein said compound is 3-{[4-(6-fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl}-2,3-dihydro[1,4]dioxino[2,3-b]pyridine or a pharmaceutically acceptable salt thereof.

EVIDENCE APPENDIX

series part 2

SSRIs: BEYOND DEPRESSION

Beyond depression: Evaluation of newer indications and off-label uses for SSRIs

Kelly C. Lee, PharmD,
Mitchell D. Feldman, MD, MPhil,
and Patrick R. Finley, PharmD, BCPP

Abstract

Although selective serotonin reuptake inhibitors (SSRIs) are prescribed most often for depressive disorders, they are increasingly being used to treat a variety of anxiety disorders and other conditions and have recently gained FDA approval for a number of them. We conducted a qualitative review of the literature for evidence on the utility of SSRIs for these uses beyond depression, and we summarize our findings here. After covering various anxiety disorders in part 1 of this two-part article, this installment covers treatment of alcohol dependence, chronic pain, eating disorders, premenstrual dysphoric disorder, and sexual dysfunction. We focus on the rationale for SSRI use in these conditions, the degree of supportive clinical trial evidence for each use, and indication-specific dosing and safety considerations. We also present recommendations, based on our literature review, on the preferred and alternative SSRIs for each therapeutic use profiled. (*Formulary* 2002;37:312–19.)

As outlined in part 1 of this article (*Formulary* 2002;37: 240–51), selective serotonin reuptake inhibitors (SSRIs) have recently accumulated a range of indications beyond the treatment of depression (table 1)[1,2] and are gaining in popularity for various off-label uses. In part 1 we assessed the evidence and made recommendations concerning the use of SSRIs for a variety of anxiety disorders. In this part we turn our attention to a broader range of new uses for SSRIs: treatment of alcohol dependence, chronic pain syndromes, eating disorders, premenstrual dysphoric disorder, and sexual dysfunction.

As in part 1, we present a qualitative review of the evidence supporting these new uses. Every attempt was made to include the most significant randomized controlled trials (RCTs); however, if no RCTs are available, open-label studies are briefly summarized. Although most of the conditions discussed here are unlabeled uses for SSRIs, we attempted to categorize the drugs into first-line, second-line, and alternative agents according to the existing evidence (see table 2).

ALCOHOL DEPENDENCE

Treatment of alcohol abuse is complex, due to wide interindividual variability in response to pharmacotherapy, high rates of comorbidities with other psychiatric conditions (eg, depression and anxiety disorders), and a host of genetic and environmental variables.[3,4]

Pharmacologic agents are commonly used to treat alcohol withdrawal symptoms, but few are used to treat alcohol dependence. Although dopamine is recognized as an important neurotransmitter in drugs of abuse such as cocaine and ethanol, other neurotransmitters (such as gamma-aminobutyric acid, serotonin, and glutamate) have been found to play roles in the drug reward, craving, and relapse mechanism.[3] Studies show that animals that prefer alcohol have reduced levels of serotonin and its major metabolite, 5-hydroxy-indoleacetic acid.[5] This inverse relationship between serotonin concentration and alcohol craving may explain the rationale for using SSRIs in treating alcohol dependence.

State of the evidence. Several studies with fluoxetine, citalopram, and sertraline have suggested that these agents may be useful in reducing alcohol consumption, craving, and/or disease relapse.[6–10] In one of the largest studies (N = 101), high-dose fluoxetine (60 mg/day) in combination with weekly psychotherapy reduced alcohol consumption from baseline in alcoholic patients, but not significantly more than placebo plus psychotherapy.[6] Acute and delayed effects were seen up to 6 months after treatment, although there was no difference between fluoxetine and placebo in abstinence or delay to the first heavy drinking day. In a single-blind study, no overall difference from placebo was seen with similar doses of fluoxetine.[7] Naranjo et al[8] found that fluoxetine (60 mg/day) reduced the average and total number of daily drinks from baseline levels, but no difference from baseline was seen in the number of abstinent days at either 60 mg/day or 40 mg/day. In a separate study, fluoxetine also failed to prevent relapse in severe alcoholics, but a trend toward higher relapse rates was seen in cocaine-dependent alcoholics compared

continues on page 315

Dr. Lee is a behavioral health sciences fellow, department of clinical pharmacy; **Dr. Feldman** is associate professor of clinical medicine, department of general internal medicine; and **Dr. Finley** is associate clinical professor of pharmacy, department of clinical pharmacy, all at the University of California, San Francisco.

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with those without dual dependence.[11]

Citalopram demonstrated more favorable outcomes in increasing the percentage of abstinent days and reducing subjective symptoms of alcoholism compared with placebo,[9] but subjects in this small study were treated with 40 mg/day for only 1 week. One of the earliest studies of an SSRI for this use showed that citalopram (40 mg/day) significantly reduced the amount of alcohol consumed per day relative to baseline in nondepressed alcoholics.[12] It also tripled the number of abstinent days and significantly reduced consumption as early as a few days after initiation.[12] Another trial compared citalopram with placebo in combination with psychosocial intervention; despite promising results in the first week, citalopram failed to show differences from placebo in alcohol intake over the course of the 12-week treatment period.[13] Finally, sertraline (200 mg/day) seemed to improve drinking behavior compared with placebo in patients without a history of lifetime depression, but not in those with a past diagnosis of depression.[10]

One of the criticisms of these previous conflicting studies is that different subtypes of alcoholics may respond differently to treatment. Babor et al[14] distinguished between two types of alcoholics, type A and type B, that may explain variation in response. Type B alcoholics, considered to be at higher risk, are characterized by earlier onset of alcohol dependence, more severe dependence, a higher incidence of comorbidities such as depression, and overall poorer prognosis after treatment.

Surprisingly, the first trial that looked at subtypes of alcoholics found that fluoxetine was associated with an increase in the number of drinking days in both type A and type B subjects and in the number of drinks per day in type B subjects.[15] Recently, the same investigators administered flexible doses of sertraline, up to 200 mg/day, to type A and type B alcoholics for 12 weeks.[16] In addition to medication, all subjects received weekly 12-step facilitation therapy. Sertraline improved the percentage of days that drinks were consumed among type A alcoholics, while no improvement was seen in type B subjects in either the sertraline or placebo groups. Type A subjects who received sertraline also showed increased time to relapse compared with their type B counterparts.

Due to negative findings in clinical trials, fluoxetine does not seem to be effective in treating alcohol dependence. Moreover, fluoxetine use may actually worsen drinking behavior in type B alcoholics and therefore should be avoided in this subset of patients.[15]

Recommendations. The role of SSRIs in the treatment of alcohol dependence still requires further investigation. Opiate antagonists and disulfiram have been used with some success for alcohol dependence, although there are advantages and disadvantages with each agent.[3] SSRIs may be an alternative in patients who have failed or could not tolerate these traditional agents. In addition, SSRIs may be beneficial in patients who have concomitant diagnosis of alcohol dependence and depression. The duration of SSRI therapy for this use is uncertain, although it is highly dependent on the patient's past and current psychiatric and medical history. Higher doses of fluoxetine, citalopram, and sertraline (than those used in depression) may need to be used in alcohol dependence, based on the literature described previously.

Table 1
Available SSRIs and their FDA-approved indications

Drug	Dosage forms and strengths	Approved indications
Fluoxetine (Prozac, Sarafem, Prozac Weekly, generics)	Prozac Tablets: 10 mg Pulvules: 10, 20, and 40 mg Oral solution: 20 mg/5 ml Sarafem Pulvules: 10, 20, and 40 mg Prozac Weekly Capsules (delayed release): 90 mg Generics Tablets: 10 and 20 mg Capsules: 10, 20, and 40 mg Oral solution: 20 mg/5 ml	Depression, OCD, bulimia nervosa, PMDD
Sertraline (Zoloft)	Tablets: 25, 50, and 100 mg Oral concentrate: 20 mg/ml (must be diluted before use)	Depression, OCD, panic disorder, PTSD
Paroxetine (Paxil)	Tablets: 10, 20, 30, and 40 mg Oral suspension: 10 mg/5 ml	Depression, OCD, GAD, panic disorder, PTSD, social phobia
Fluvoxamine (Luvox, generics)	Luvox and generics Tablets: 25, 50, and 100 mg	OCD
Citalopram (Celexa)	Tablets: 20 and 40 mg Oral solution: 10 mg/5 ml	Depression

OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = posttraumatic stress disorder; GAD = generalized anxiety disorder

Formulary/Source: Adapted from references 1 and 2

CHRONIC PAIN

Historically, tricyclic antidepressants (TCAs) have proven fairly effective for the management of various chronic pain syndromes, including migraine headaches, diabetic neuropathy, and others. Their pharmacologic effect for these conditions is believed to be independent of antidepressant properties, occurs

■ Table 2
Summary of recommendations for reviewed uses/indications*

Alcohol dependence	No recommendation
Chronic pain	
Diabetic neuropathy	■ First line—no recommendation ■ Second line—citalopram, paroxetine
Fibromyalgia	■ First line—no recommendation ■ Second line—fluoxetine
Headache syndromes	■ First line—no recommendation ■ Second line—fluoxetine, fluvoxamine ■ Alternative—citalopram, paroxetine, sertraline
Eating disorders	
Bulimia nervosa	■ First line—fluoxetine ■ Second line—fluvoxamine
Anorexia nervosa	■ First line—no recommendation ■ Second line—fluoxetine
Binge-eating disorder	■ First line—no recommendation ■ Second line—fluoxetine, sertraline
Premenstrual dysphoric disorder	■ First line—citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Sexual dysfunction	
Premature ejaculation	■ First line—no recommendation ■ Second line—paroxetine ■ Alternative—citalopram, fluoxetine, fluvoxamine, sertraline

* **First line** = Agents that are FDA-approved for the indication and/or have an adequate number of well-designed randomized controlled trials (RCTs) and good tolerability. **Second line** = Agents with a few RCTs limited by inadequate design/small sample size or a large number of open-label studies suggesting efficacy, and/or with less tolerability than first-line agents or inconvenient dosing for the indication. **Alternative** = Agents with no published RCTs, no supportive evidence from RCTs, or only a few supportive open-label studies; these agents also have significant problems with administration or tolerability for the indication. Agents within each recommendation category are listed in alphabetical order.

Formulary/Source: K.C. Lee, PharmD, M.D. Feldman, MD, and P.R. Finley, PharmD

at comparatively lower doses, and has a relatively rapid onset. While most experts feel that antidepressants that enhance norepinephrine and serotonin are most effective, some preliminary evidence suggests that SSRIs may have a role in managing certain types of chronic pain.[17]

Headache syndromes. Seven double-blind, placebo-controlled trials have been published that collectively suggest that SSRIs may relieve migraine or tension headache syndromes (three studies with fluoxetine, two with fluvoxamine, and one each with citalopram and paroxetine).[18–24] Only two of these studies compared an SSRI (citalopram or fluvoxamine) with a TCA (amitriptyline).[21,22] While both fluvoxamine and amitriptyline reduced migraine attacks in the one trial,[22] results of the other study favored the dual-action TCA over citalopram.[21]

Additional open-label or retrospective trials with SSRIs have reported benefits, however, including two studies among patients in whom treatment with TCAs and monoamine oxidase inhibitors had failed.[25,26] While the precise role of SSRIs in managing headache pain remains undefined, this preliminary evidence may prompt additional studies comparing SSRIs and TCAs.

Diabetic neuropathy. Several studies have evaluated the analgesic effects of SSRIs in treating diabetic neuropathy. One notable crossover study reported that the TCA amitriptyline (average dose of 105 mg/day) was considerably more effective than fluoxetine (40 mg daily), as the two agents yielded moderate or greater pain relief in 74% and 48% of patients, respectively.[27] Investigations comparing paroxetine with TCAs have shown similar efficacy between these agents, although the beneficial effects of the SSRI were only evident once higher plasma concentrations were achieved.[28,29] A small placebo-controlled study of citalopram (40 mg/day) demonstrated mild to moderate pain relief that did not appear to be associated with plasma concentrations of the drug.[30]

Other types of chronic pain. Preliminary investigations of SSRIs for other pain syndromes have met with mixed results. For the treatment of fibromyalgia, fluoxetine and amitriptyline both appeared to be significantly more effective than placebo and exhibited superior effects when administered together.[31] A placebo-controlled study of citalopram (20 to 40 mg/day) failed to reveal statistically significant differences in fibromyalgia outcomes.[32] Fluoxetine (20 mg/day) was reported to be comparable to amitriptyline for treating low back pain in one study[33] and superior to amitriptyline for treatment of rheumatic pain in another.[34] In contrast, citalopram was found to be much less effective for low back pain than the noradrenergic antidepressant maprotiline.[35] Clearly, definition of the SSRIs' role in managing chronic pain awaits future well-controlled investigations in nondepressed patient populations.

EATING DISORDERS

Shortly after fluoxetine's launch in this country, a variety of case reports began documenting weight loss in depressed subjects. These reports generated considerable optimism about the anorectic properties of SSRIs. Long-term studies ultimately showed that most patients returned to their baseline body weight with chronic fluoxetine administration. As a class, SSRIs are now considered to be weight-neutral, with the notable exception of paroxetine, which has been shown to induce significant weight gain (defined as an increase of 7% or more)

in approximately 25% of depressed patients.[36] Nonetheless, SSRIs have been used with variable success to treat other eating disorders.

Bulimia nervosa. Although psychotherapy is generally regarded as the treatment of choice for bulimia nervosa, a wide variety of antidepressants appear to be quite helpful as adjunctive treatment for reducing binge-eating behavior. Among the SSRIs, fluoxetine has shown the most promise and is, in fact, the only SSRI to gain FDA approval for this indication. Short- and long-term studies have shown that fluoxetine can reduce binge-eating behavior,[37,38] and this effect is generally believed to be independent of effects on mood. While the relationship of dose to response in bulimia has not been extensively studied, one investigation found superior response rates and good tolerability with fluoxetine doses of 60 mg daily as compared with 20 mg daily or placebo.[39] The only other SSRI to be evaluated for the management of bulimia has been fluvoxamine, which was found to significantly reduce relapse rates compared with placebo.[40]

Anorexia nervosa. The therapeutic effects of SSRIs on anorexia nervosa have not been forthcoming. While hospitalization remains the most efficacious intervention for reestablishing healthy nutritional status, this option is obviously expensive, prompting the search for other remedies. Early efforts to treat anorexia with antidepressants met with disappointing results, but more recent studies have shown SSRIs to be quite effective, particularly if administered after weight restoration has occurred.[41,42] One potential explanation for this response pattern is that anorexic patients do not have sufficient dietary intake or body stores of serotonin precursors (ie, l-tryptophan) at baseline to support the basic pharmacologic action of antidepressants. Subsequent studies of fluoxetine in patients who have regained their ideal body weight have reported comparatively high remission rates and reductions in obsessive and compulsive behavior.

Binge-eating disorder. While binge-eating behaviors are always associated with bulimia nervosa and sometimes encountered with anorexia nervosa, binge-eating disorder is a distinct psychiatric condition distinguished from other eating disorders by the absence of compensatory weight loss measures (eg, vomiting, laxative abuse). The evidence supporting SSRI benefits specifically for binge-eating disorder is very limited. In a 6-week study, McElroy et al reported a significant reduction in binge-eating behavior with sertraline as compared with placebo, as well as improvement in overall psychopathology; the average daily sertraline dose was 189 mg.[43] In a 52-week placebo-controlled study of obese patients, fluoxetine (in combination with behavioral therapy) was found to be much more effective at inducing weight loss than behavioral therapy alone.[44] There was no difference in benefit, however, among patients who had binge-eating histories and those who did not.[44]

■ While fluoxetine is the only SSRI approved for premenstrual dysphoric disorder, all have demonstrated efficacy in published trials.

PREMENSTRUAL DYSPHORIC DISORDER

Premenstrual dysphoric disorder (PMDD) is widely recognized as a distinct and cyclical mental illness that afflicts 3% to 8% of women, exclusively during their reproductive years. It is considered a more severe form of premenstrual syndrome (PMS) and is associated with a high degree of social and occupational impairment.[45] By definition, the physical and mental symptoms of PMDD are manifest during the luteal phase and remit shortly after the onset of menses.

The pathophysiology of PMDD remains unclear. Most women with PMDD, for instance, have quantitatively normal fluctuations in gonadal hormones, but their response to the cyclic changes is most pronounced. As the diagnostic criteria for PMDD contain many symptoms suggestive of depressive or anxiety disorders, a serotonin deficiency has been theorized as a final common pathway.[46] Acute dietary depletion of a serotonin precursor (l-tryptophan) has been shown to aggravate premenstrual symptoms, and the superior efficacy of serotonergic antidepressants in treating PMDD further supports this explanation.[47]

Treatment of PMDD is largely contingent on the severity or urgency of symptoms. While mild illness may respond to exercise, dietary modification, or calcium supplementation, more severe symptoms appear to be uniquely responsive to SSRIs (or other serotonergic agents).

State of the evidence. To date, more than 40 studies have been published documenting the efficacy of SSRIs for relief of physical symptoms (eg, headache, bloating, breast tenderness) as well as mood fluctuations (eg, irritability, anxiety, melancholia). A recent meta-analysis of 15 RCTs studying SSRIs for the treatment of severe PMS concluded that this antidepressant class was significantly more effective than placebo in reducing overall PMS symptoms, with an overall mean difference of −1.066 in favor of SSRIs (95% CI, −1.38 to −0.75), corresponding to an odds ratio of 6.9.[48]

Recommendations. While fluoxetine is the only SSRI approved by the FDA for this indication, all have demonstrated efficacy in published trials.[48]

Although the benefit of SSRIs for PMDD has been demonstrated in short- and long-term studies, the onset of therapeutic effects is much more rapid than that reported for depression. Statistically significant differences in baseline symptoms have been demonstrated within 3 to 4 days of treatment initiation,[49] implying that the mechanism responsible for PMDD relief may be subtly distinct from that for depression. Blinded studies have also shown that these benefits may be achieved even if the SSRI is administered only during

the 7- to 14-day period immediately before menses (ie, the intermittent to late luteal phase).[49,50] This dosing method may be preferred from the standpoint of cost as well as advantages in tolerability and medication adherence.

The doses of SSRIs used in PMDD studies have been comparable to those used for depression. In a seminal study of fluoxetine, for instance, 20 mg/day was comparable in efficacy to 60 mg/day, but the higher dose was associated with a much higher dropout rate due to adverse effects.[51] Anecdotal reports of poor tolerability with SSRIs among women with PMDD have not been confirmed in fixed-dose trials, but future studies of low-dose SSRI therapy are clearly indicated.

The duration of SSRI treatment for PMDD is always patient-specific and largely influenced by the presence or absence of environmental triggers (eg, domestic issues, dietary imbalances, overall health status). It should be emphasized, however, that the therapeutic benefits of SSRIs will be lost immediately upon discontinuation (in contrast to treatment termination for depressive illness). Furthermore, PMDD symptoms often worsen over time until relief is ultimately provided by the onset of menopause.

SEXUAL DYSFUNCTION

Sexual dysfunction is a common and disruptive condition associated with depression as well as with SSRI therapy. While SSRIs are commonly implicated for difficulty achieving orgasm, depression itself has been associated with a decrease in libido for more than 50% of patients.[52] Therefore, certain aspects of sexual function (ie, libido) may actually improve with the onset of an SSRI's therapeutic antidepressant effects.

Of these two types of sexual dysfunction, the influence of SSRIs on orgasm is much more notorious and problematic. Approximately 30% to 50% of patients receiving any SSRI report a significant delay in orgasm or ejaculation. Although most patients find delayed orgasm to be an undesirable effect, this side effect can serve to successfully treat men suffering from premature ejaculation (often defined as an intravaginal ejaculatory latency time [IELT] of less than 60 seconds).[53] At least four double-blind, placebo-controlled studies have shown SSRI treatment to successfully prolong time to ejaculation in men with documented premature ejaculation.[54–57] Studies of single-dose administration have found that while all SSRIs can prolong latency time, paroxetine has the most profound effect, increasing the IELT by more than 600%, on average.[57] Ejaculatory delay with SSRIs appears to be a dose-dependent phenomenon; with the exception of one positive open-label investigation with low-dose sertraline (25 mg), low doses have not been vigorously studied.[58]

CONCLUSION

Among the newer uses of SSRIs reviewed in this second installment of our two-part article, only premenstrual dysphoric disorder and bulimia nervosa have consistently been shown to be effectively treated with SSRIs. There is less evidence for the use of SSRIs in alcohol dependence, chronic pain syndromes (diabetic neuropathy, fibromyalgia, headache syndromes, low back pain), anorexia nervosa, and binge-eating disorder. The efficacy and tolerability of SSRIs in these latter uses need to be further investigated with randomized, placebo-controlled trials. While SSRIs appear to be beneficial in treating premature ejaculation, their association with undesirable orgasm delay in other patients leaves their role in sexual dysfunction highly subject to individual patient circumstances.

Although clinicians may be compelled to choose one SSRI over another based on FDA-approved labeling, a patient's psychiatric and medical history, concurrent medications, and preference should also be considered, as well as the tolerability profile and cost of individual SSRIs.

DISCLOSURE

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REFERENCES

1. Drug Facts and Comparisons. St. Louis: Facts and Comparisons. a Wolters Kluwer Co; 2002.
2. McEvoy GK. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2001.
3. Anton RF. Pharmacologic approaches to the management of alcoholism. J Clin Psychiatry 2001:62(Suppl 20):11-7.
4. Pettinati HM. The use of selective serotonin reuptake inhibitors in treating alcoholic subtypes. J Clin Psychiatry 2001:62(Suppl 20):26-31.
5. LeMarquand D, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: Findings of animal studies. Biol Psychiatry 1994; 36:395–421.
6. Kranzler HR, Burleson JA, Korner P, et al. Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 1995;152:391-7.
7. Gorelick DA, Paredes A. Effect of fluoxetine on alcohol consumption in male alcoholics. Alcohol Clin Exp Res 1992;16:261-5.
8. Naranjo CA, Kadlec KE, Sanhueza P, et al. Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. Clin Pharmacol Ther 1990;47:490–8.
9. Naranjo CA, Poulos CX, Bremner KE, Lanctot KL. Citalopram decreases desirability, liking, and consumption of alcohol in alcohol-dependent drinkers. Clin Pharmacol Ther 1992; 51:729-39.
10. Pettinati HM, Volpicelli JR, Luck G, et al. Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol 2001;21:143-53.
11. Kabel DI, Petty F. A placebo-controlled, double-blind study of fluoxetine in severe alcohol dependence: Adjunctive pharmacotherapy during and after inpatient treatment. Alcohol Clin Exp Res 1996;20:780–4.
12. Naranjo CA, Sellers EM, Sullivan JT, et al. The serotonin uptake inhibitor citalopram attenuates ethanol intake. Clin Pharmacol Ther 1987;41: 266-74.
13. Naranjo CA, Bremner KE, Lanctot KL. Effects of citalopram and a brief psycho-social intervention on alcohol intake, dependence and problems. Addiction 1995;90:87-99.
14. Babor TF, Dolinsky ZS, Meyer RE, et al. Types of alcoholics: Concurrent and predictive validity of some common classification schemes. Br J Addict 1992;87:1415-31.
15. Kranzler HR, Burleson JA, Brown J, Babor TF. Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. Alcohol Clin Exp Res 1996;20:1534–41.
16. Pettinati HM, Volpicelli JR, Kranzler HR, et al. Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. Alcohol Clin Exp Res 2000;24:1041-9.
17. Ansari A. The efficacy of newer antidepressants in the treatment of chronic pain: A review of current literature. Harv Rev Psychiatry 2000;7:257-77.
18. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. Headache 1992;32:101–4.
19. Saper JR, Silberstein SD, Lake AE III, Winters ME. Double-blind trial of fluoxetine: Chronic daily headache and migraine. Headache 1994;34: 497-502.
20. d'Amato CC, Pizza V, Marmolo T, et al. Fluoxetine for migraine prophylaxis: A double-blind trial. Headache 1999;39:716-9.
21. Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. J Neurol Neurosurg Psychiatry

1996;61:285-90.
22. Bank J. A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. Headache 1994;34:476-8.
23. Manna V, Bolino F, Di Cicco L. Chronic tension-type headache, mood depression and serotonin: Therapeutic effects of fluvoxamine and mianserine. Headache 1994;34:44-9.
24. in the treatment of chronic tension-type headache. An explanatory double-blind trial. Headache 1994;34:20-4.
25. Diamond S, Freitag FG. The use of fluoxetine in the treatment of headache. Clin J Pain 1989;5:200-1.
26. Foster CA, Bafaloukos J. Paroxetine in the treatment of chronic daily headache. Headache 1994;34:587-9.
27. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326: 1250-6.
28. Sindrup SH, Gram LF, Brosen K, et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990;42:135-44.
29. Sindrup SH, Grodum E, Gram LF, Beck-Nielsen H. Concentration-response relationship in paroxetine treatment of diabetic neuropathy symptoms: A patient-blinded dose-escalation study. Ther Drug Monit 1991;13:408-14.
30. Sindrup SH, Bjerre U, Dejgaard A, et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clin Pharmacol Ther 1992;52:547-52.
31. Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arth Rheum 1996;39:1852-9.
32. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain 1995;61:445-9.
33. Schreiber S, Vinokur S, Shavelzon V, et al. A randomized trial of fluoxetine versus amitriptyline in musculo-skeletal pain. Isr J Psychiatry Relat Sci 2001;38:88-94.
34. Rani PU, Naidu MU, Prasad VB, et al. An evaluation of antidepressants in rheumatic pain conditions. Anesth Analg 1996;83:371-5.
35. Atkinson JH, Slater MA, Wahlgren DR, et al. Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity. Pain 1999;83:137-45.
36. Fava M, Judge R, Hoog SL, et al. Fluoxetine versus sertraline and paroxetine in major depressive disorder: Changes in weight with long-term treatment. J Clin Psychiatry 2000;61:863-7.
37. Mitchell JE, Fletcher L, Hanson K, et al. The relative efficacy of fluoxetine and manual-based self-help in the treatment of outpatients with bulimia nervosa. J Clin Psychopharmacol 2001; 21:298-304.
38. Goldstein DJ, Wilson MG, Thompson VL, et al. Long-term fluoxetine treatment of bulimia nervosa. Fluoxetine Bulimia Nervosa Research Group. Br J Psychiatry 1995;166:660-6.
39. Fluoxetine in the treatment of bulimia nervosa. A multicenter, placebo-controlled, double-blind trial. Fluoxetine Bulimia Nervosa Collaborative Study Group. Arch Gen Psychiatry 1992;49:139-47.
40. Fichter MM, Kruger R, Rief W, et al. Fluvoxamine in prevention of relapse in bulimia nervosa: Effects on eating-specific psychopathology. J Clin Psychopharmacol 1996;16:9-18.
41. Kaye WH, Weltzin TE, Hsu LK, Bulik CM. An open trial of fluoxetine in patients with anorexia nervosa. J Clin Psychiatry 1991;52:464-71.
42. Kaye WH, Nagata T, Weltzin TE, et al. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. Biol Psychiatry 2001; 49:644-52.
43. McElroy SL, Casuto LS, Nelson EB, et al. Placebo-controlled trial of sertraline in the treatment of binge eating disorder. Am J Psychiatry 2000;157:1004-6.
44. Marcus MD, Wing RR, Ewing L, et al. A double-blind, placebo-controlled trial of fluoxetine plus behavior modification in the treatment of obese binge-eaters and non-binge-eaters. Am J Psychiatry 1990;147:876-81.
45. Ling FW. Recognizing and treating premenstrual dysphoric disorder in the obstetric, gynecologic, and primary care practices. J Clin Psychiatry 2000;61(Suppl 12):9-16.
46. Steiner M, Pearlstein T. Premenstrual dysphoria and the serotonin system: Pathophysiology and treatment. J Clin Psychiatry 2000;61(Suppl 12):17-21.
47. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: A randomized controlled trial. Arch Gen Psychiatry 1999;56:932-9.
48. Dimmock PW, Wyatt KM, Jones PW, O'Brien PM. Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: A systematic review. Lancet 2000;356:1131-6.
49. Wikander I, Sundblad C, Andersch B, et al. Citalopram in premenstrual dysphoria: is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? J Clin Psychopharmacol 1998; 18:390-8.
50. Jermain DM, Preece CK, Sykes RL, et al. Luteal phase sertraline treatment for premenstrual dysphoric disorder. Results of a double-blind, placebo-controlled, crossover study. Arch Fam Med 1999;8:328-32.
51. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. N Engl J Med 1995;332:1529-34.
52. Casper RC, Redmond DE Jr., Katz MM, et al. Somatic symptoms in primary affective disorder. Presence and relationship to the classification of depression. Arch Gen Psychiatry 1985;42:1098-104.
53. Gelenberg AJ, Delgado P, Nurnberg HG. Sexual side effects of antidepressant drugs. Curr Psychiatry Rep 2000;2:223-7.
54. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: A double-blind, randomized, placebo-controlled study. Am J Psychiatry 1994;151:1377-9.
55. Kara H, Aydin S, Yucel M, et al. The efficacy of fluoxetine in the treatment of premature ejaculation: A double-blind placebo controlled study. J Urol 1996;156:1631-2.
56. Mendels J, Camera A, Sikes C. Sertraline treatment for premature ejaculation. J Clin Psychopharmacol 1995;15:341-6.
57. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: A double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. J Clin Psychopharmacol 1998;18:274-81.
58. Swartz DA. Sertraline hydrochloride forpremature ejaculation. J Urol 1994;151:345A. **F**

Off-Label Applications for SSRIs

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Selective serotonin reuptake inhibitors (SSRIs) are widely used because of their safety, tolerability, and demonstrated efficacy across a broad range of clinical conditions. Medical literature supports the use of SSRIs for the treatment of many conditions outside of the indications approved by the U.S. Food and Drug Administration. SSRIs offer a reasonable alternative to traditional therapy for generalized anxiety disorder. A side effect of SSRIs coincidentally provides therapy for premature ejaculation. SSRIs may reduce the frequency and severity of migraine headaches and are possibly effective in reducing the pain of diabetic neuropathy. When taken in combination with tricyclic antidepressants, SSRIs offer more potent therapy for fibromyalgia than either agent alone. SSRIs appear to be effective in some patients with neurocardiogenic syncope that is refractory to standard therapies. Clinical experience supported by ongoing research continues to expand on the broad array of therapeutic applications for this class of medication. (Am Fam Physician 2003;68:498-504.

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Selective serotonin reuptake inhibitors (SSRIs) were initially developed to relieve depression and have become the most commonly prescribed class of antidepressants.[1] SSRIs block the reuptake of serotonin at the presynaptic neuron, with minimal or no effect on norepinephrine or dopamine. This narrow mechanism of action confers similarity of efficacy and tolerability with few side effects.[1]

The following five SSRIs have been approved by the U.S. Food and Drug Administration (FDA) for use in the United States: citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft). Although the FDA has approved these SSRIs for treatment of a variety of conditions, the medical literature supports their use for a number of "off-label" indications. Off-label use does not imply improper or illegal use.[2] The FDA cannot give approval for further indications until it has reviewed new efficacy and safety data provided by the pharmaceutical companies.

The use of a well-documented therapy that lacks a specific "labeling" should not be precluded. The decision to prescribe a given medication should be based on the available evidence and a careful consideration of the potential risks and benefits in the context of the individual patient.

This article reviews the use of SSRIs for six conditions commonly managed by family physicians: generalized anxiety disorder, premature ejaculation, migraine headache, diabetic neuropathy, fibromyalgia, and neurocardiogenic syncope *(Table 1)*.[3-20]

See page 406 for definitions of strength-of-evidence levels.

See editorial on page 425.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is one of the most prevalent psychiatric disorders. Benzodiazepines such as diazepam (Valium), alprazolam (Xanax), and clonazepam (Klonopin), which are used to treat GAD, can cause sedation, difficulty concentrating, and other bothersome side effects. Dependence can develop, leading to withdrawal symptoms on discontinuation of these agents. Buspirone (BuSpar), a nonbenzodiazepine anxiolytic that does not lead to dependence, is an effective alternative, but it must be taken three times daily.[21]

SSRIs have been prescribed safely and effectively for mixed anxiety and depression syndromes, as well as for social anxiety.[22] Paroxetine may be effective for GAD treatment.[5] [Evidence level A, randomized controlled trial (RCT)]

TABLE 1
Off-Label Applications of SSRIs

Condition	*Medication and recommended dosages*	*Efficacy/recommendations*	*Level of evidence*
Generalized anxiety disorder	Fluvoxamine (Luvox), 50 to 300 mg daily[3,4]	Effective; may be a good long-term alternative to benzodiazepines or other anxiolytics	A: RCT
	Paroxetine (Paxil), 20 to 60 mg daily (generalized anxiety disorder is not an off-label use)[5]	—	A: RCT
Premature ejaculation	Paroxetine, 20 mg daily or as needed a few hours before anticipated sexual activity[6,7]	Effective; consider as first-line treatment	A: RCT
	Sertraline (Zoloft), 25 to 50 mg daily or as needed a few hours before anticipated sexual activity[6,8,9]		
	Fluoxetine (Prozac), 20 mg daily[6]		
Migraine headaches (prophylaxis)	Fluoxetine, 20 to 40 mg daily[10-12]	May be useful if patient cannot use standard prophylactic agents or if other agents fail; good choice if patient has concomitant depression or other illness treatable with SSRI	A: RCT
Diabetic neuropathy	Paroxetine, 40 mg daily[13]	Possibly effective; other drugs should be considered first. One meta-analysis found no difference between placebo and SSRIs.	B: lower quality RCT
Fibromyalgia	Fluoxetine, 20 mg daily[14,15]	Possibly effective, particularly when combined with amitriptyline (Elavil)	B: lower quality RCT
	Citalopram (Celexa), 20 to 40 mg daily[16,17]	Studies on citalopram showed no significance	B: lower quality RCT
Neurocardiogenic syncope	Paroxetine, 20 mg daily[18]	May be useful if standard treatments fail	A: RCT
	Sertraline, 50 mg daily[19]	Has been studied in children	B: nonrandomized, small, prospective trial
	Fluoxetine, 20 mg daily[20]	—	B: nonrandomized, small, prospective trial

SSRIs = selective serotonin reuptake inhibitors; RCT = randomized controlled trial.

Information from references 3 through 20.

Delayed or inhibited ejaculation, a known side effect of SSRIs, has made SSRIs potentially useful in the management of premature ejaculation.

In the trial,[5] 81 patients were randomized to treatment with paroxetine (20 mg daily), imipramine (Tofranil), or the benzodiazepine 2'chlordesmethyldiazepam. The patients had a diagnosis of GAD according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed (DSM-IV), a score of at least 18 on the Hamilton Rating Scale for Anxiety (HRSA), and no comorbid psychiatric conditions. The patients ranged from 18 to 65 years of age. Demographics were similar in each group. Sixty-three patients (77.7 percent) completed the study. Using the HRSA to measure response, 68 percent of the patients in the paroxetine group, 72 percent in the imipramine group, and 55 percent in the 2'chlordesmethyldiazepam group had at least a 50 percent decrease in HRSA score by the end of the eight-week study. Paroxetine was recently approved by the FDA for GAD treatment.

SSRIs may be particularly useful in the treatment of GAD in pediatric patients.[3] [Evidence level A, RCT] In a multicenter, double-blind trial, 128 children six to 17 years of age with social phobia, separation anxiety disorder, or GAD (as defined by DSM-IV) were randomized to treatment with fluvoxamine or placebo.[3] All had received three weeks of psychotherapy without showing improvement. Fluvoxamine was chosen because it was the only SSRI approved by the FDA for use in children in 1996 when the study was designed. Fluvoxamine therapy (at a maximum dosage of 300 mg daily) resulted in a statistically significant decrease in scores on the Pediatric Anxiety Rating Scale compared with placebo. Although this trial was not specific to GAD, it was noted that anxiety disorders in children typically occur together, thereby making it difficult to isolate one disorder for study.

SSRIs seem particularly suited for use in older patients with anxiety disorders.[4] [Evidence level B, nonrandomized trial] In a small, open-label trial, patients more than 50 years of age with GAD, panic disorder, or obsessive-compulsive disorder were treated with fluvoxamine (median dose, 200 mg daily).[4] Twelve of 19 patients (63 percent) completed the 21-week study, with eight of the 12 (66.6 percent) achieving a 50 percent reduction in symptoms as measured by standardized scales. The existence of comorbid depression, as well as the confounding variable of therapy combined with benzodiazepines, were two further limitations of this trial. The authors conclude that randomized, placebo-controlled trials are warranted to study the use of SSRIs for treatment of anxiety disorders in the older population.

Premature Ejaculation

Though premature ejaculation has been overshadowed by recent attention given to erectile dysfunction, it is the most prevalent form of male sexual dysfunction.[2,3] Delayed or inhibited ejaculation, a known side effect of SSRIs, has made SSRIs potentially useful in the treatment of this disorder. The ejaculation-delaying effect was analyzed in a double-

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blind, placebo-controlled trial completed by 51 men.[6] Fluoxetine, sertraline, and paroxetine have been found to increase the latent period of intravaginal ejaculation and therefore to be beneficial in patients who prematurely ejaculate.[6] [Evidence level A, RCT] Fluvoxamine had the least effect in increasing ejaculatory latency, a difference that was not statistically significant compared with placebo. Citalopram was not studied.

It was demonstrated in a second study[6] that SSRI-induced ejaculation delay is probably an effect independent of the baseline ejaculatory latency time.

In a study of 46 men 22 to 63 years of age who prematurely ejaculate (with a baseline mean ejaculatory interval of less than one minute), sertraline increased the ejaculatory interval in a dose-dependent fashion.[8] At 25 mg daily, sertraline increased the mean ejaculatory interval to 7.6 minutes with the fewest side effects and with no men experiencing anejaculation. At 50 mg daily, the mean ejaculatory interval increased to 13.1 minutes with four men experiencing anejaculation and two men experiencing minor side effects (drowsiness, anorexia, dyspepsia). At 100 mg daily, the mean ejaculatory interval increased to 16.4 minutes, but 10 men experienced anejaculation and two men experienced erectile dysfunction and decreased libido.

Studies also show that SSRIs, particularly sertraline[9] and paroxetine,[7] can probably be used on an as-needed basis and taken a few hours before anticipated sexual activity. [Reference 9—Evidence level B, nonrandomized trial; Reference 7—Evidence level B, randomized crossover trial]

Migraine Headache Prophylaxis

There is fair support for the effectiveness of SSRIs in migraine prophylaxis. Prophylactic treatments for migraine headaches have included tricyclic antidepressants, beta-adrenergic blockers, and calcium channel blockers. These medications are frequently associated with an unfavorable side effect profile and may not be well tolerated by a significant number of patients with migraines. Because most theories of migraine pathophysiology focus on altered serotonergic metabolism, and given the favorable tolerability of SSRIs, the use of SSRIs in migraine prophylaxis has been studied.[10-12,24] While published results are promising, most authors acknowledge that these studies are only preliminary.

Three randomized, double-blind, placebo-controlled studies showed a decrease in the frequency and severity of migraine headaches with fluoxetine therapy.

Most studies used fluoxetine. Of these, at least four were randomized, double-blind, placebo-controlled studies.[10-12,24] Three of these four studies showed a significant decrease ($P < .05$) in the frequency and severity of headaches.[10-12] [References 10, 11, and 12—Evidence level A, RCT] The patients ranged from 18 to 65 years of age, and the minimum frequency of migraines ranged from more than one per month to more than one per week. Daily dosages of fluoxetine ranged from 20 to 40 mg in these studies.

Evidence is limited regarding the use of the other SSRIs in migraine headache treatment. One randomized comparison study of fluvoxamine and amitriptyline (Elavil) showed that fluvoxamine decreased the number of migraine attacks as effectively as amitriptyline.[25] [Evidence level B, double-blind comparison]

Diabetic Neuropathy

Tricyclic antidepressants are well established as effective therapy for the symptoms of diabetic neuropathy.[26,27] Although mexiletine (Mexitil), capsaicin (Zostrix), carbamazepine (Tegretol), and gabapentin (Neurontin) are among other therapies that have been shown to be effective in treating neuropathic pain, no single medication has proved to be consistently effective.[28-31] SSRIs should not be considered as first-line therapy for diabetic neuropathy; the

SSRIs should not be considered as first-line therapy for diabetic neuropathy, because the evidence for their use for this purpose is limited.

evidence for their use is fair and indicates that SSRIs may be only possibly effective.

A randomized, double-blind, crossover study of 29 patients found both imipramine (50 to 75 mg daily) and paroxetine (40 mg daily) to be superior to placebo.[13] [Evidence level B, lower quality RCT] Imipramine, however, was significantly better than paroxetine for relieving nearly all symptoms, including pain and sleep disturbance.

However, one study did not find SSRIs to be superior to placebo in relieving painful neuropathy.[32] [Evidence level A, meta-analysis] The meta-analysis of RCTs compared the efficacy and adverse effects of antidepressants and anticonvulsants in treating neuropathic pain, including diabetic neuropathy. Overall, for every three patients treated with a tricyclic antidepressant or an anticonvulsant, one experienced a 50 percent reduction in pain (number needed to treat [NNT] of three). While the authors noted the lack of statistically significant improvement using the pooled data of SSRIs, they thought the data insufficient to "draw a robust conclusion."[32]

Another review of RCTs found SSRIs to be helpful in treating diabetic neuropathy but confirmed that they are not as efficacious as other therapies.[33] [Evidence level B, nonquantitative systematic review] An NNT of 1.4 was calculated for imipramine, compared with the NNT of 2.4 calculated from other studies of tricyclic antidepressants. The NNT was 1.9 for dextromethorphan (Delsym), 3.3 for carbamazepine, 3.4 for tramadol (Ultram) and levodopa (Larodopa), 3.7 for gabapentin, 5.9 for capsaicin, 6.7 for SSRIs, and 10.0 for mexiletine. It was cautioned that, with the exception of the tricyclic antidepressants, these numbers were calculated on the basis of few trials or small total patient numbers per drug.

Fibromyalgia

Fibromyalgia is the most common rheumatic cause of chronic pain.[34] Medications most commonly prescribed are tricyclic antidepressants, SSRIs, muscle relaxants, simple analgesics, and nonsteroidal anti-inflammatory drugs.[35] Pharmacologic therapies have shown only modest benefit at best. A meta-analysis of 49 studies found exercise and cognitive behavior therapy to be more efficacious than pharmacologic treatment alone.[36] [Evidence level A, meta-analysis] The results of the few RCTs involving SSRIs have been mixed.

Two small trials of citalopram (20 to 40 mg daily) failed to reach significance, although there were subtle trends toward improvements in sleep, pain, and functioning.[16,17] [References 16 and 17—Evidence level B, lower quality RCTs] A trial of fluoxetine (20 mg daily) did not show significant improvement after six weeks of therapy, but the study was limited by a 43 percent dropout rate from an initially small sample of 42 patients.[14] [Evidence level B, lower quality RCT]

Conversely, a crossover, placebo-controlled trial comparing fluoxetine (20 mg daily) and amitriptyline (25 mg daily) demonstrated significant improvement in global well-being, pain, and sleep for each medication alone, and further improved efficacy when the two were used in combination.[15] [Evidence level B, lower quality RCT] Nineteen of 31 initial participants (61 percent) completed each of four six-week trials separated by two-week washout periods. Significant improvement was noted by 63 percent of those taking the combination compared with 32 percent and 24 percent of patients taking a single agent. The effects were independent of coexistent depression. The study was limited by the dropout rate and has not been duplicated.

Although the Cochrane Musculoskeletal Group is performing a systematic review to

assess the efficacy of SSRIs versus placebo and other antidepressants, it is clear that further study is necessary.[37] Currently, SSRIs, with or without tricyclic antidepressants, can be viewed as only possibly effective in patients with unsatisfactory responses to nonpharmacologic therapy.

Neurocardiogenic Syncope

SSRIs appear to be an effective treatment in neurocardiogenic syncope refractory to standard therapies. Neurocardiogenic syncope, or vasovagal syncope, is a common disorder of transient autonomic nervous system dysfunction.[38] Although no definitive treatment for neurocardiogenic syncope exists, standard therapies such as atenolol (Tenormin) and midodrine (ProAmatine) have demonstrated efficacy. Fludrocortisone (Florinef) and increased salt and fluid intake are commonly used as well.[38]

One randomized, double-blind, placebo-controlled study involved the use of paroxetine in the treatment of neurocardiogenic syncope refractory to standard therapies.[18] [Evidence level A, RCT] Paroxetine (20 mg daily) was found to significantly improve symptoms in patients refractory to or intolerant of standard treatments. Of the 68 patients in the study, all of whom had a documented positive head-up tilt test initially, 61.8 percent in the paroxetine group versus 38.2 percent in the placebo group had negative tilt table tests after one month. During the approximately two-year follow-up period, spontaneous syncope occurred in 17.6 percent in the paroxetine group compared with 52.9 percent in the placebo group. Paroxetine was generally well tolerated.

Smaller, nonrandomized, prospective studies (two involving pediatric patients) involved the use of sertraline and fluoxetine in the treatment of refractory neurocardiogenic syncope.[19,20,39] Each of these agents showed promising results, with most patients having a negative repeat tilt test or remaining symptom-free for at least six months.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Navy Medical Corps or the U.S. Navy at large.

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REFERENCES

1. Kroenke K, West SL, Swindle R, Gilsenan A, Eckert GJ, Dolor R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. JAMA 2001;286:2947-55.
2. American Academy of Pediatrics. Unapproved uses of approved drugs: the physician, the package insert, and the Food and Drug Administration: subject review. Pediatrics 1996;98:143-5.
3. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. The research unit on pediatric psychopharmacology anxiety study group. N Engl J Med 2001;344:1279-85.
4. Wylie ME, Miller MD, Shear MK, Little JT, Mulsant BH, Pollock BG, et al. Fluvoxamine pharmacotherapy of anxiety disorders in later life: preliminary open-trial data. J Geriatr Psychiatry Neurol 2000; 13:43-8.
5. Rocca P, Fonzo V, Scotta M, Zanalda E, Ravizza L. Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand 1997;95: 444-50.
6. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. J Clin Psychopharmacol 1998;18:274-81.
7. McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. J Urol 1999;161:1826-30.
8. McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride. Int J Impot Res 1998;10:181-4.
9. Kim SW, Paick JS. Short-term analysis of the effects of as needed use of sertraline at 5 PM for the treatment of premature ejaculation. Urology 1999;54:544-7.
10. Adly C, Staumanis J, Chesson A. Fluoxetine prophylaxis of migraine. Headache 1992;32:101-4.
11. d'Amato CC, Pizza V, Marmola T, Giordano E, Alfano V, Nasta A. Fluoxetine for migraine prophylaxis: a double-blind trial. Headache 1999;39:716-9.
12. Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia 1998;18: 283-6.
13. Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990;42:135-44.

14. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 1994;23:255-9.
15. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996;39: 1852-9.
16. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia—a randomized, double-blind, placebo-controlled study. Eur J Pain 2000;4:27-35.
17. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain 1995;61:445-9.
18. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 1999;33:1227-30.
19. Grubb BP, Samoil D, Kosinski D, Kip K, Brewster P. Use of sertraline hydrochloride in the treatment of refractory neurocardiogenic syncope in children and adolescents. J Am Coll Cardiol 1994;24:490-4.
20. Grubb BP, Wolfe DA, Samoil D, Temesy-Armos P, Hahn H, Elliott L. Usefulness of fluoxetine hydrochloride for prevention of resistant upright tilt induced syncope. Pacing Clin Electrophysiol 1993;16:458-64.
21. Goa KL, Ward A. Buspirone. A preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. Drugs 1986;32:114-29.
22. Kent JM, Coplan JD, Gorman JM. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. Biol Psychiatry 1998;44:812-24.
23. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999;281:537-44.
24. Saper JR, Silberstein SD, Lake AE 3rd, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache 1994;34:497-502.
25. Bank J. A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. Headache 1994;34:476-8.
26. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987;37: 589-96.
27. Sindrup SH, Gram LF, Skjold T, Grodum E, Brosen K, Beck-Nielsen H. Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. Br J Clin Pharmacol 1990;30:683-91.
28. Oskarsson P, Ljunggren JG, Lins PE. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy: The Mexiletine Study Group. Diabetes Care 1997;20:1594-7.
29. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin: a meta-analysis. Eur J Clin Pharmacol 1994;46:517-22.
30. Gomez-Perez FJ, Choza R, Rios JM, Reza A, Huerta E, Aguilar CA, et al. Nortriptyline-fluphenazine vs. carbamazepine in the symptomatic treatment of diabetic neuropathy. Arch Med Res 1996;27:525-9.
31. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831-6.
32. Collins SL, Moore RA, McQuay HJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manage 2000; 20:449-58.
33. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389-400.
34. Freundlich B, Leventhal L. Diffuse pain syndromes. In: Klippel JH, Weyand CM, Wortmann R, eds. Primer on the rheumatic diseases. 11th ed. Atlanta, Ga.: Arthritis Foundation, 1997.
35. Leventhal LJ. Management of fibromyalgia. Ann Intern Med 1999;131:850-8.
36. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med 1999;21:180-91.
37. Riera R, Rodriguez-Martin JL. Specific serotonin uptake inhibitors versus placebo or antidepressants for fibromyalgia (protocol for a Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.
38. Calkins H. Pharmacologic approaches to therapy for vasovagal syncope. Am J Cardiol 1999;84(8A): 20Q-25Q.
39. Lenk M, Alehan D, Ozme S, Celiker A, Ozer S. The role of serotonin re-uptake inhibitors in preventing recurrent unexplained childhood syncope—a preliminary report. Eur J Pediatr 1997;156:747-50.

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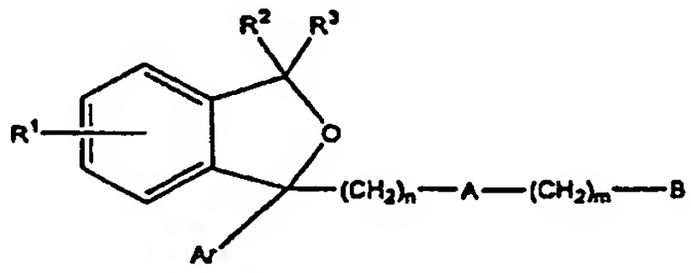

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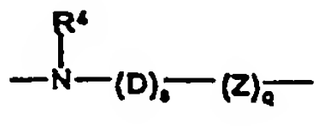

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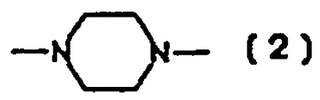

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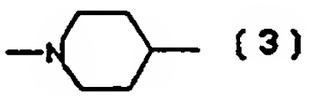

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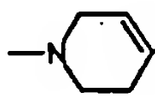

(4)

(57) Abstract

The present invention relates to benzofuran derivatives having general Formula (I). A is selected from (1), (2), (3), (4) wherein: Z is O or S; s is 0 or 1; q is 0 or 1; R^4 is hydrogen, C_{1-6}–alkyl, C_{2-6}–alkenyl, C_{2-6}–alkynyl, C_{1-6}–alkyl–Aryl, or C_{1-6}–alkyl–O–Aryl; D is a spacer group selected from branched or straight chain C_{1-6}–alkylene, C_{2-6}–alkenylene and C_{2-6}–alkynylene; its enantiomers, and pharmaceutically acceptable acid addition salt thereof. The compounds are potently binding to the 5–HT_{1A} receptor.

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Benzofuran derivatives, their preparation and use

The present invention relates to novel benzofuran derivatives potently binding to the 5-HT_{1A} receptor, pharmaceutical compositions containing these compounds and the use thereof for the treatment of certain psychiatric and neurological disorders. Many of the compounds of the invention are also potent serotonin reuptake inhibitors and are considered to be particularly useful for the treatment of depression.

Background Art

Clinical studies of known 5-HT_{1A} partial agonists such as e.g. buspirone, ipsapirone and gepirone have shown that 5-HT_{1A} partial agonists are useful in the treatment of anxiety disorders such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder (Glitz, D. A., Pohl, R., *Drugs* 1991, *41*, 11). Preclinical studies indicate that full agonists also are useful in the treatment of the above mentioned anxiety related disorders (Schipper, *Human Psychopharm.*, 1991, *6*, S53).

There is also evidence, both clinical and preclinical, in support of a beneficial effect of 5-HT_{1A} partial agonists in the treatment of depression as well as impulse control disorders and alcohol abuse (van Hest, *Psychopharm.*, 1992, *107*, 474; Schipper et al, *Human Psychopharm.*, 1991, *6*, S53; Cervo et al, *Eur. J. Pharm.*, 1988, *158*, 53; Glitz, D. A., Pohl, R., *Drugs* 1991, *41*, 11; Grof et al., *Int. Clin. Psychopharmacol.* 1993, *8*, 167-172; Ansseau et al., *Human Psychopharmacol.* 1993, *8*, 279-283).

5-HT_{1A} agonists and partial agonists inhibit isolation-induced aggression in male mice indicating that these compounds are useful in the treatment of aggression (Sanchéz et al, *Psychopharmacology*, 1993, *110*, 53-59).

Furthermore, 5-HT_{1A} agonists have been reported to show activity in animal models predictive for antipsychotic effects (Wadenberg and Ahlenius, *J. Neural. Transm.*, 1991, *83*, 43; Ahlenius, *Pharmacol. & Toxicol.*, 1989, *64*, 3; Lowe et al., *J. Med. Chem.*, 1991, *34*, 1860; New et al., *J. Med. Chem.*, 1989, *32*, 1147; and Martin et al., *J. Med. Chem.*,

1989, *32*, 1052) and may therefore be useful in the treatment of psychotic disorders such as schizophrenia. Recent studies also indicate that 5-HT_{1A} receptors are important in the serotonergic modulation of haloperidol-induced catalepsy (Hicks, *Life Science* 1990, *47*, 1609) suggesting that 5-HT_{1A} agonists are useful in the treatment of the side effects induced by conventional antipsychotic agents such as e.g. haloperidol.

5-HT_{1A} agonists have shown neuroprotective properties in rodent models of focal and global cerebral ischaemia and may, therefore, be useful in the treatment of ischaemic disease states (Prehn , *Eur. J. Pharm.* 1991, *203*, 213).

Pharmacological studies have been presented which indicate that 5-HT_{1A} antagonists are useful in the treatment of senile dementia (Bowen et al., Trends Neur. Sci. 1992, *15*, 84).

An overview of 5-HT_{1A} antagonists and proposed potential therapeutic targets for these antagonists based upon preclinical and clinical data are presented by Schechter et al., *Serotonin*, 1997, Vol.2, Issue 7. It is stated that 5-HT_{1A} antagonists may be useful in the treatment of schizophrenia, dementia associated with Alzheimer's disease, and in combination with SSRI antidepressants also to be useful in the treatment of depression.

Both in animal models and in clinical trials it has been shown that 5-HT_{1A} agonists exert antihypertensive effects *via* a central mechanism (Saxena and Villalón, *Trends Pharm. Sci.* 1990, *11*, 95; Gillis *et al*, *J. Pharm. Exp. Ther.* 1989, *248*, 851). 5-HT_{1A} ligands may, therefore, be beneficial in the treatment of cardiovascular disorders.

5-HT reuptake inhibitors are well known antidepressant drugs and useful for the treatment of panic disorders and social phobia.

The effect of combined administration of a compound that inhibits serotonin reuptake and a 5-HT_{1A} receptor antagonist has been evaluated in several studies (Innis, R.B. et al., *Eur. J. Pharmacol.*, **1987**, *143, p 195-204* and Gartside, S.E., *Br. J. Pharmacol.* **1995**, *115, p 1064-1070*, Blier, P. *et al, Trends Pharmacol. Sci.* **1994**, *15*, 220). In these studies it was found that 5-HT_{1A} receptor antagonists would abolish the initial brake on 5-HT

neurotransmission induced by the serotonin reuptake inhibitors and thus produce an immediate boost of 5-HT transmission and a more rapid onset of therapeutic action.

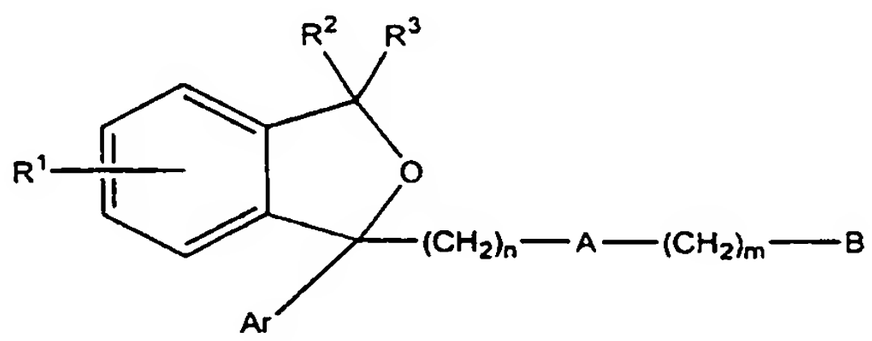
Several patent applications have been filed which cover the use of a combination of a 5-HT_{1A} antagonist and a serotonin reuptake inhibitor for the treatment of depression (see EP-A2-687 472 and EP-A2-714 663).

Accordingly, agents acting on the 5-HT_{1A} receptor, both agonists and antagonists, are believed to be of potential use in the therapy of psychiatric and neurological disorders and thus being highly desired. Furthermore, antagonists at the same time having potent serotonin reuptake inhibition activity may be useful for the treatment of depression.

Summary of the Invention

It has now been found that compounds of a certain class of benzofuran derivatives bind to the 5-HT_{1A} receptor with high affinities. Furthermore, it has been found that many of these compounds have potent serotonin reuptake inhibition activity.

Accordingly, the present invention relates to novel compounds of the general Formula I:



(I)

wherein

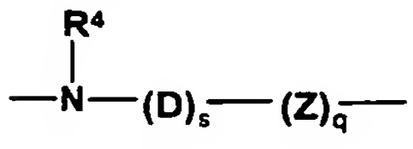
R^1 is hydrogen, halogen, trifluoromethyl, trifluoromethylsulfonyloxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, hydroxy, formyl, acyl, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, acylamino, C_{1-6} alkoxycarbonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, C_{2-12} dialkylaminocarbonylamino, nitro, cyano, COOH, or COO-C_{1-6} alkyl;

R^2 and R^3 are each independently selected from hydrogen, trifluoromethyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl and C_{1-6} alkoxy;

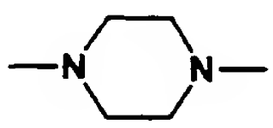
n is 1, 2, 3, 4 or 5;

m is 0 or 1;

A is selected from the following groups:



(1)



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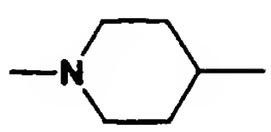

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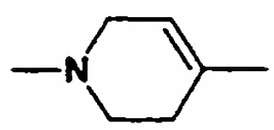


(4)

wherein

Z is O or S;

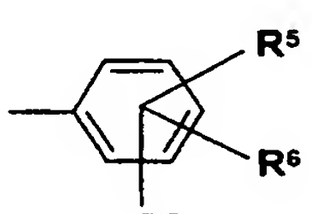
s is 0 or 1;

q is 0 or 1;

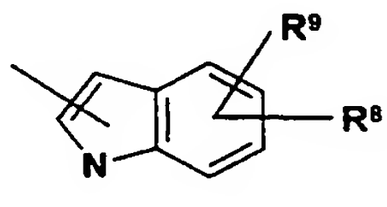
R^4 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkyl-Aryl, or C_{1-6}-alkyl-O-Aryl,

D is a spacer group selected from branched or straight chain C_{1-6}-alkylene, C_{2-6}-alkenylene and C_{2-6}-alkynylene;

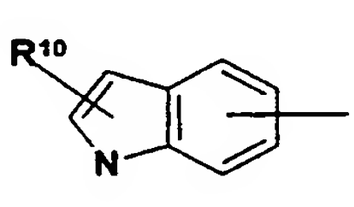
B is a group selected from a group of formula (II), (III), and (IV)



(II)



(III)



(IV)

wherein R^5, R^6, R^7, R^8, R^9 and R^{10} are each independently selected among the R^1 substituents;

or R^8 and R^9 together form a fused 5- or 6-membered ring optionally containing further heteroatoms;

or two of the groups of R^5, R^6 and R^7 are linked together thereby forming a $—O—(CH_2)_p—O—$ -bridge wherein p is 1 or 2;

Ar and Aryl are independently selected from the group consisting of phenyl, 2–thienyl, 3–thienyl, 2–furanyl, 3–furanyl, 2–pyrimidyl, 1–indolyl, 2–indolyl, 3–indolyl, indol-2-on-1-yl, indol-2-on-3-yl, 2- or 3–benzofuranyl, 2- or 3–benzothiophenyl, 1–naphthyl or 2–naphthyl, each optionally substituted with halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy, C_{1-6} alkylsulfonyl, cyano, trifluoromethyl, trifluoromethylsulfonyloxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl–C_{1-6} alkyl, nitro, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, acylamino or alkylenedioxy;

its enantiomers, and pharmaceutically acceptable acid addition salt thereof.

In one embodiment of the invention A is a group of formula (1) and the other substituents are as defined above.

In another embodiment of the invention A is a group of formula (2) and the other substituents are as defined above.

In a third embodiment of the invention A is a group of formula (3) and the other substituents are as defined above.

In a fourth embodiment of the invention A is a group of formula (4) and the other substituents are as defined above.

Thus in a preferred embodiment of the invention A is a group of formula (1) and R^4 is methyl, ethyl, propyl, prop-2-en-1-yl, 2-furylmethyl, or 2-phenoxyethyl; q = 0; or A is a group of formula (1) and Z is O and the other substituents are as defined above.

In a further embodiment of the invention, B is a group of formula (II), preferably a alkoxysubstituted phenyl, a benzodioxan group or a 1,2-methylenedioxybenzene group and the other substituents are as defined above.

In a further embodiment of the invention, B is a group of formula (III), preferably a 3-indolyl group and the other substituents are as defined above.

In a further embodiment of the invention, B is a group of formula (III), preferably a 3-indolyl group and the substituents R^8 and R^9 are preferably selected from hydrogen, methyl, fluoro, chloro, bromo, iodo, *t*-butyl or *i*-propyl in the 5-position; or fluoro, chloro or carboxy in the 7-position; or by 5,7-difluoro, 4-fluoro-7-methyl or 4-chloro-7-methyl; or the two substituents together form a pyridyl ring fused to the 3-indolyl.

In a further embodiment of the invention, B is a group of formula (IV) and the other substituents are as defined above.

Ar is preferably phenyl or phenyl substituted with halogen or CF_3, most preferably substituted with F or Cl in the 4-position or Cl or CF_3 in the 3-position.

R^1 is preferably H, CN or F in the 5-position of the isobenzofuran group.

R^2 and R^3 are preferably selected from hydrogen or methyl.

n is preferably 2, 3 or 4.

m is preferably 0.

In a preferred embodiment of the invention n = 2, 3 or 4; R^2 and R^3 are both hydrogen; R^1 is H, CN or F in the 5-position of the isobenzofuran group; and Ar is phenyl which may be substituted with F or Cl in the 4-position or with Cl or CF_3 in the 3-position and the other substituents are as defined above.

In another preferred embodiment of the invention, A is a group of formula (1); q = 0; R^4 is methyl; D is propylene; m = 0; and B is a 1,4-benzodioxan group of Formula (II) attached in the 5-position and the other substituents are as defined above.

In another preferred embodiment of the invention, A is a group of formula (1); R^4 is CH_3 or prop-2-en-1-yl; n = 3; D is ethylene or propylene; and B is a phenyl group wherein at least one substituent is OMe and the other substituents are as defined above.

In a further embodiment of the invention, A is a group of formula (1); q is 0; R^4 is methyl, ethyl, propyl, 2-propen-1-yl, 2-furylmethyl or 2-phenoxyethyl; D is ethylene, propylene or butylene; m = 0; and B is a 3-indolyl group of Formula (III) and the other substituents are as defined above.

In another preferred embodiment of the invention, A is a group of formula (2) or (3); n = 3; m = 0; and B is an 4- or 5-indolyl-group of Formula (IV) wherein R^{10} is hydrogen; R^1 is CN in the 5-position of the isobenzofuran and Ar is 4-Fluorophenyl and the other substituents are as defined above.

The invention also relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier or diluent.

In a further embodiment, the invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the effect of 5-HT_{1A} receptors.

In particular, the invention relates to the use of a compound according to the invention or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of depression, psychosis, anxiety disorders, panic disorder, obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders or social phobia.

In still another embodiment, the present invention relates to a method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the effect of 5-HT_{1A} receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

The compounds of the invention have high affinity for the 5-HT_{1A} receptor. Accordingly, the compounds of the invention are considered useful for the treatment of depression, psychosis, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders and social phobia.

Due to their combined antagonism of 5-HT_{1A} receptors and serotonin reuptake inhibiting effect, many of the compounds of the invention are considered particularly useful as fast onset of action medicaments for the treatment of depression. The compounds may also be useful for the treatment of depression in patients who are resistant to treatment with currently available antidepressants.

Detailed Description of the Invention

Some of the compounds of general Formula I may exist as optical isomers thereof and such optical isomers are also embraced by the invention.

The term C_{1-6} alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6} alkenyl and C_{2-6} alkynyl, respectively, designate such groups having from two to six carbon atoms, inclusive.

Halogen means fluoro, chloro, bromo, or iodo.

The term C_{3-8} cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The terms C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, designate such groups in which the alkyl group is C_{1-6} alkyl as defined above.

Acyl means -CO-alkyl wherein the alkyl group is C_{1-6} alkyl as defined above.

C_{1-6} alkylamino means -NH-alkyl, and C_{2-12} dialkylamino means -N-(alkyl)$_2$ where the alkyl group is C_{1-6} alkyl as defined above.

Acylamino means -NH-acyl wherein acyl is as defined above.

C_{1-6} alkoxycarbonylamino means alkyl-O-CO-NH- wherein the alkyl group is C_{1-6} alkyl as defined above.

C_{1-6} alkylaminocarbonylamino means alkyl-NH-CO-NH- wherein the alkyl group is C_{1-6} alkyl as defined above.

C_{2-12} dialkylaminocarbonylamino means (alkyl)$_2$-N-CO-NH- wherein the alkyl group is C_{1-6} alkyl as defined above.

Exemplary of organic acid addition salts according to the invention are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of inorganic acid addition salts according to the invention are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids. The acid addition salts of the invention are preferably pharmaceutically acceptable salts formed with non-toxic acids.

Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (e.g. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

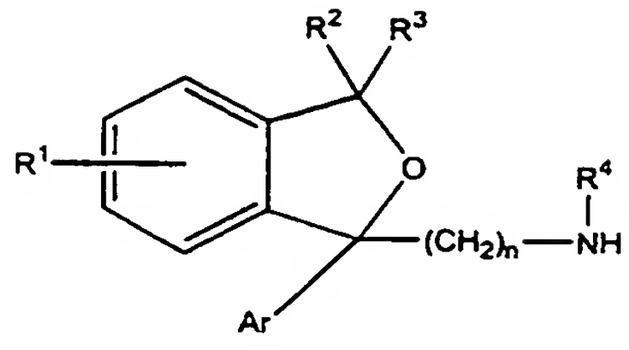
Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

The compounds of the invention can be prepared by one of the following methods comprising:

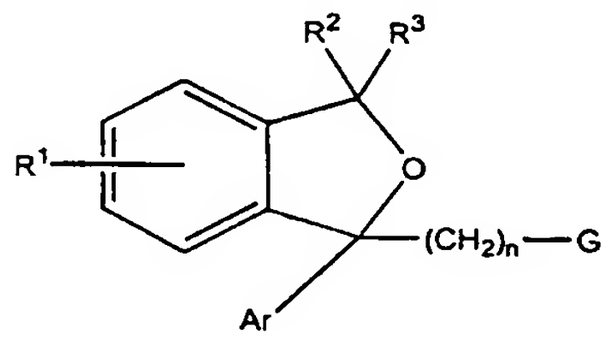
a) alkylating an amine of formula



(V)

wherein R^1, R^2, R^3, R^4, n and Ar are as defined above with an alkylating agent of formula $G-(D)_s-(Z)_q-(CH_2)_m-B$ wherein D, Z, m, s, q and B are as defined above and G is a suitable leaving group such as halogen, mesylate, or tosylate;

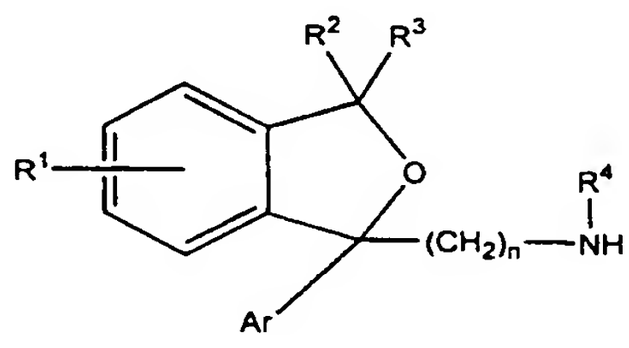
b) alkylating an amine of formula $H-A-(CH_2)_m-B$ wherein A, m and B are as defined above with an alkylating agent of formula



(VI)

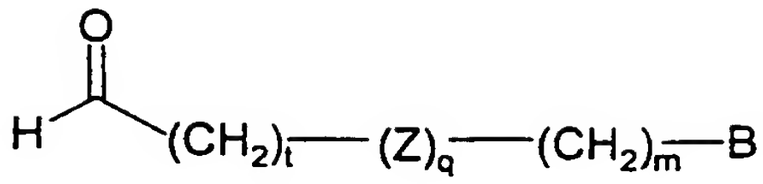
wherein R^1, R^2, R^3, n and Ar are as defined above and G is a suitable leaving group such as halogen, mesylate, or tosylate;

c) reductive alkylation of an amine of formula



(VII)

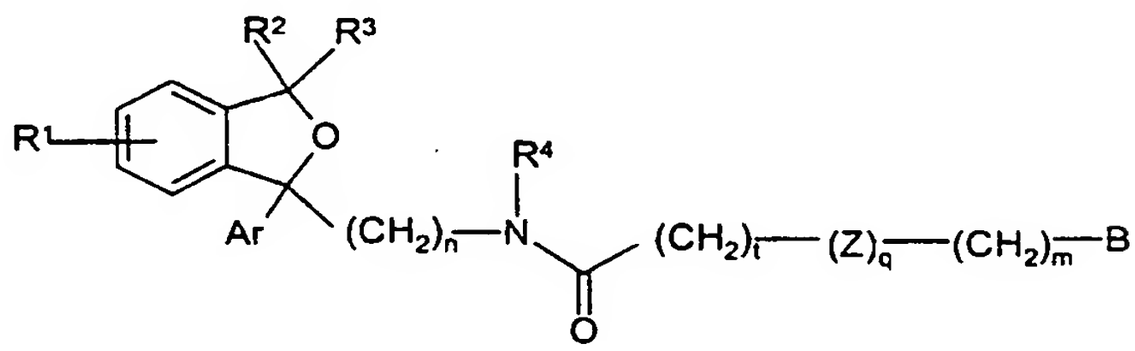
wherein R^1, R^2, R^3, R^4, n and Ar are as defined above with an aldehyde of formula



(VIII)

wherein Z, m, q and B are as defined above and t is 1-5;

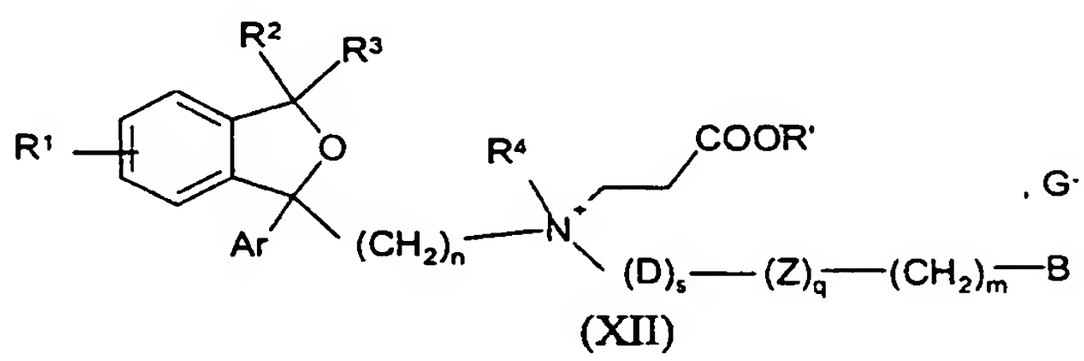
d) reducing an amide of formula



(XI)

wherein R^1, R^2, R^3, R^4, n, q, Ar, Z, m and B are as defined above and t is 1-5;

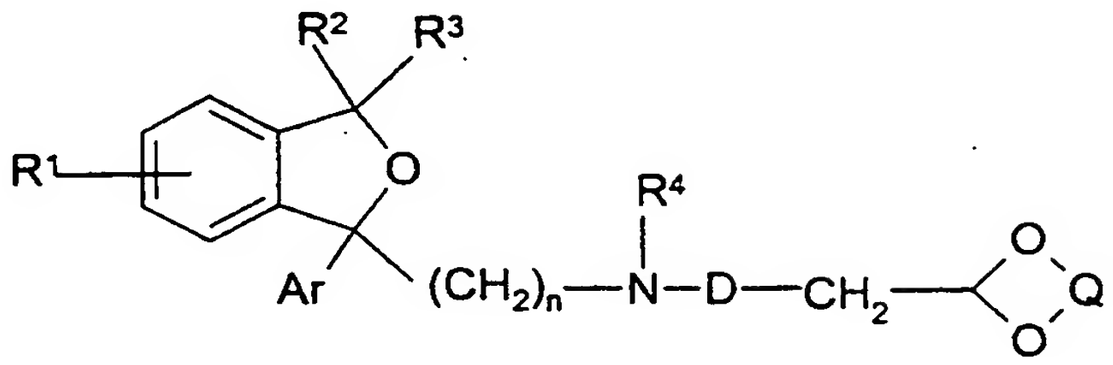
e) releasing final product by the means of Hofmann elimination from a resin of formula



(XII)

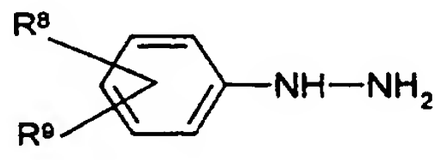
wherein R^1, R^2, R^3, R^4, n, s, q, Ar, D, Z, m and B are as defined above, G is as defined above; and HOR' is a hydroxy substituted resin such as cross linked hydroxymethylpolystyrene or Wang resin.

f) reacting a compound of the formula



XIII

wherein R^1, R^2, R^3, R^4, Ar, D and N are as defined above; $(OH)_2Q$ is a diol such as substituted ethylene glycol or propylene glycol, or a polymer bound diol, with a hydrazine of formula



XIV

wherein R^8 and R^9 is as defined above, using Lewis acids as catalyst.

The alkylations according to Methods a and b are generally performed by boiling the reactants under reflux or by heating them at a fixed temperature in a suitable solvent such as acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, ethanol, 2-propanol, ethyl acetate, N,N-dimethylformamide, dimethyl sulfoxide or 1-methyl-2-pyrrolidinone in the presence of a base such as triethylamine or potassium carbonate. Amines of formula V are prepared by means of demethylation according to the method described by Bigler et al, Eur. J. Med. Chem. Chim. Ther, 1977, 12, 289-295, or by the methods outlined in examples 14 and 15. The starting materials used in example 14 were prepared as described in example 9 or from readily available compounds by standard methods. The enantiomers of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile used as starting material for the demethylation are prepared as described in EP patent No. 347066. The alkylating agents of formula $G-(D)_s-(Z)_q-(CH_2)_m-B$ are

commercially available, prepared by methods obvious to the chemist skilled in the art or prepared as exemplified in Examples 5-8. Ethyl 1,4-benzodioxan-5-carboxylate used as starting material in Example 5 is prepared by methods obvious to the chemist skilled in the art from the corresponding carboxylic acid prepared according to literature (Fuson et al., J. Org. Chem., 1948, 13, 489). Alkylating agents of formula VI are prepared from the corresponding dimethylamine (Formula VI: G = $N(Me)_2$) as exemplified in example 9. The secondary amines of formula H-A-$(CH_2)_m$-B are commercially available, prepared by methods obvious to the chemist skilled in the art or prepared according to literature procedures. 1-(2-methoxyphenyl)piperazine is prepared according to Pollard et al., J. Org. Chem., 1958, 23, 1333. [2-(2-Methoxyphenoxy)ethyl]methylamine and [2-(3-methoxyphenoxy)ethyl]-methylamine are prepared as exemplified in Examples 7 and 10 using commercially available 2-methoxyphenoxyacetic acid and 3-methoxyphenoxyacetic acid, respectively, as starting materials.

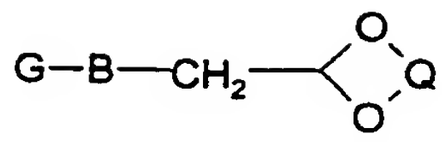
The reductive alkylations according to method c and d are performed according to standard literature methods using $NaCNBH_3$, $NaBH_4$ or $NaBH(OAc)_3$ as reducing agent in a suitable solvent.

The reductions according to Methods e and f are generally performed by use of $LiAlH_4$, AlH_3 or diborane in an inert solvent such as tetrahydrofuran, dioxane, or diethyl ether at room temperature or at a slightly elevated temperature.

The release of final products by means of Hofmann elimination in Method g is generally performed by the use of an organic base such as triethylamine or diisopropylethylamine in an aprotic organic solvent such as dichloromethane, toluene or N,N-dimethylformamide. The polymer of formula XII is prepared in a synthesis sequence as exemplified in Example 4 and described in the following. The starting acryl ester resin ($CH_2CHC(O)OR'$) is prepared according to literature procedures (Brown et al., J. Am. Chem. Soc., 1997, 119, 3288-95) by acylation of commercially available hydroxy substituted resins such as cross linked hydroxymethylpolystyrene or Wang resin with acryloyl chloride. Secondary amines of formula H_2N-D-Z-$(CH_2)_m$-B are introduced by Michael addition in an organic solvent

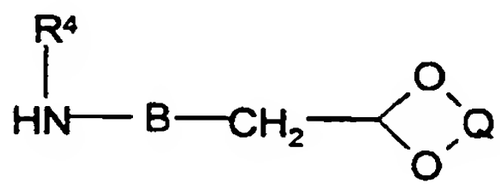
such as N,N-dimethylformamide at ambient temperature. The secondary amines used are either commercially available, prepared by methods obvious to the chemist skilled in the art or prepared according to literature procedures. 3-(2-Methoxyphenyl)propylamine is prepared according to Leeson et al., J. Med. Chem. 1988, 31, 37-54, 3-(3-methoxyphenyl)propylamine according to Meise et al. Liebigs Ann. Chem., 1987, 639-42, 3-(2-methoxyphenoxy)propylamine according to Augsein et al., J. Med. Chem., 1965, 8, 356-67, 3-(3-methoxyphenoxy)propylamine according to Bremner et al., Aust. J. Chem. 1984, 37, 129-41, 2-benzyloxyethylamine according to Harder et al. Chem. Ber. 1964, 97, 510-19, 2-(1*H*-indolyl-3-yl)ethylamine according to Nenitzescu et al., Chem. Ber., 1958, 91, 1141-45 and 3-(1*H*-indolyl-3-yl)propylamine according to Jackson et al., J. Am. Chem. Soc., 1930, 52, 5029. The second diversifying group is introduced by means of alkylation with an agent of formula VI by boiling the reactants under reflux or by heating them at a fixed temperature in a suitable solvent such as tetrahydrofuran, dioxane, ethanol, 2-propanol, ethyl acetate, N,N-dimethylformamide, dimethyl sulfoxide or 1-methyl-2-pyrrolidinone in the presence of a soluble base such as diisopropylethylamine or triethylamine, or by means of reductive alkylation with an aldehyde of formula IX using standard solid phase synthesis literature methods using $NaCNBH_3$, $NaBH_4$ or $NaBH(OAc)_3$ as reducing agent in a suitable solvent. The third diversifying group was introduced by means of quarternisation using an alkylating agent of formula R^4-G in an organic solvent such as tetrahydrofuran, dioxane, ethanol, 2-propanol, ethyl acetate, N,N-dimethylformamide, dimethyl sulfoxide or 1-methyl-2-pyrrolidinone at ambient temperature giving resins of formula XII.

The indole formation according to method h is performed by the reaction of acetals of formula XIII with aryl hydrazines of formula XIV resulting in the corresponding hydrazones, which subsequently are converted into indoles by means of the Fischer indole synthesis. The synthesis sequence is preferably performed as a one-pot procedure using a Lewis acid catalysts, preferably zinc chloride or boron fluoride, or protic acids, preferably sulfuric acid or phosphoric acid, in a suitable solvent such as acetic acid or ethanol at an elevated temperature. Acetals of formula XIII are prepared by alkylation of secondary amines of formula V with acetals of formula XV



XV

using the conditions described above for methods a and b. Alternatively, the acetals of formula XIII are prepared by alkylation of acetals of formula XVI



XVI

with an alkylating agent of formula VI using the conditions described above for methods a and b. The acetals of formula XVI are prepared by reaction of acetals of formula XV with primary amines of formula NH_2R^4 using standard conditions.

Polymer bound acetals of formula XV is prepared by reaction of aldehydes of formula G-B-CH_2CHO with commercially available 2,2-dimethyl-1,3-dioxolan-4-yl-methoxymethyl polystyrene in a suitable solvent such as toluene, using p-toluenesulfonic acid as catalyst at elevated temperature. 4-Chlorobutanal, 5-chloropentanal, and 6-chlorohexanal were prepared in analogy to the method described by Normant et al., Tetrahedron 1994, 50 (40), 11665.

Examples

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Mass spectra were obtained on a Quattro MS-MS system from VG Biotech, Fisons Instruments. The MS-MS system was connected to an HP 1050 modular HPLC system. A volume of 20-50 µl of the sample (10 µg/ml) dissolved in a mixture of 1% acetic acid in acetonitril/water 1:1 was introduced via the autosampler at a flow of 30 µl/min into the Electrospray Source. Spectra were obtained at two standard sets of operating conditions.

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (50 X 4.6

mm YMC ODS-A with 5 µm particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times R_t are expressed in minutes.

One set to obtain molecular weight information (MH+) (21 eV) and the other set to induce fragmentation patterns (70 eV). The background was subtracted. The relative intensities of the ions are obtained from the fragmentation pattern. When no intensity is indicated for the Molecular Ion (MH+), this ion was only present under the first set of operating conditions. Preparative LC-MS-separation was performed on the same instrument. The LC conditions (50 X 20 mm YMC ODS-A with 5 µm particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet. NMR signals corresponding to acidic protons are generally omitted. Content of water in crystalline compounds was determined by Karl Fischer titration. Standard workup procedures refer to extraction with the indicated organic solvent from proper aqueous solutions, drying of combined organic extracts (anhydrous $MgSO_4$ or Na_2SO_4), filtering and evaporation of the solvent *in vacuo*. For column chromatography silica gel of type Kieselgel 60, 230-400 mesh ASTM was used.

Example 1

(+)-1-[3-[[4-(1,4-Benzodioxan-5-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**1a**). A mixture of 5-(4-bromobutyl)-1,4-benzodioxane (1.5 g, 5.5 mmol), (+)-1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (2.2. g, 5.5 mmol), potassium carbonate (3.0 g, 22

mmol), and methyl isobutyl ketone (150 mL) was boiled under reflux for 16 h. After cooling to room temperature the organic phase was washed with water (150 mL), the solvents evaporated *in vacuo* and the remaining oil purified by column chromatography (ethyl acetate/heptane/triethylamine 75:20:5) affording 2.0 g (73%) of the title compound as an oil: $[\alpha]^{22}_D$ + 8.93° (c 0.5; CH_3OH). ^1H NMR ($CDCl_3$) δ 1.25-1.35 (m, 1H), 1.40-1.60 (m, 5H), 2.05-2.30 (m, 9H), 2.55 (t, 2H), 4.20-4.30 (m, 4H), 5.10-5.20 (m, 2H), 6.65-6.75 (m, 3H), 7.00 (t, 2H), 7.35 (d,1H), 7.40 (dd, 2H), 7.50 (s, 1H), 7.60 (d, 1H); MS m/z 501 (MH+, 100), 262 (27), 149 (77), 109 (52).

The following compounds were prepared analogously:

(+)-1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate (**1b**): mp 114-16°C (ethyl acetate);$[\alpha]^{22}_D$ + 8.96° (c 1.0; CH_3OH); ^1H NMR (DMSO-d_6) δ 1.35-1.45 (m, 1H),1.45-1.55 (m, 1H), 1.80 (m, 2H), 2.20-2.30 (m, 2H), 2.45-2.55 (m, 2H), 2.60 (s, 3H), 2.90 (m, 2H), 2.95 (m, 2H), 4.20-4.30 (m, 4H), 5.20 (m, 2H), 6.65-6.75 (m, 3H), 7.10-7.20 (m, 2H), 7.55-7.60 (m, 2H), 7.70-7.80 (m, 1H), 7.80-7.95 (m, 2H); MS m/z 488 (MH+, 100), 262 (33), 149 (52), 109 (55).

1-[3-[[2-(1,4-Benzodioxan-5-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate (**1c**): mp 118-20°C (ethyl acetate); ^1H NMR (DMSO-d_6) δ 1.40-1.70 (m, 2H), 2.25 (t, 2H), 2.70 (s, 3H), 2.75-2.90 (m, 2H), 2.90-3.15 (m, 4H), 4.15-4.30 (m, 4H), 5.20 (m, 2H), 6.65-6.80 (m, 3H), 7.20 (t, 2H), 7.60 (dd, 2H), 7.70-7.85 (m, 3H); MS m/z 473 (MH+, 64), 323 (13), 262 (24), 163 (100), 109 (25).

1-[3-[[1,4-Benzodioxan-5-ylmethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate (**1d**): mp 160-62 °C (acetone/methanol); ^1H NMR (DMSO-d_6) δ 1.40-1.70 (m, 2H), 2.25 (t, 2H), 2.60 (s, 3H), 2.90 (t, 2H), 4.00 (s, 2H), 4.20-4.30 (m, 4H), 5.20 (m, 2H), 6.80-7.00 (m, 3H), 7.15 (t, 2H), 7.50 – 7.65 (dd, 2H), 7.70-7.85 (m, 3H); MS m/z 459 (MH+, 7), 109 (100).

Example 2

1-(4-Fluorophenyl)-1-[3-[4-(2-methoxyphenyl)piperazinyl]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**2a**). A mixture of 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (2.5 g, 7.9 mmol), 1-(2-methoxyphenyl)piperazine (2.0 g, 10.4 mmol), potassium carbonate (3 g, 22 mmol) and methyl isobutyl ketone (200 mL) was boiled under reflux for 16 h. After cooling to room temperature the organic phase was washed with water (200 mL), the solvents were evaporated *in vacuo* and the remaining oil purified by column chromatography (ethyl acetate/heptane/triethylamine 75:20:5). The title compound crystallised from diethyl ether 1.5 g (40 %): mp 147-49 °C; ^{1}H NMR (DMSO-d_6) δ 1.30-1.65 (m, 2H), 2.10-2.30 (m, 2H), 2.40 (t, 2H), 2.50-2.70 (m, 4H), 2.90-3.20 (m, 4H), 3.85 (s, 3H), 5.20 (m, 2H), 6.70-7.10 (m, 6H), 7.30-7.55 (m, 4H), 7.60 (d, 1H); MS m/z, 472 (MH+, 100), 262 (14), 109 (19).

The following compounds were prepared analogously:

1-(4-Fluorophenyl)-1-[3-[[2-(2-methoxyphenoxy)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**2b**): (oil) ^{1}H NMR ($CDCl_3$) δ 1.30-1.40 (m, 1H), 1.40-1.55 (m, 1H), 2.10-2.20 (m, 2H), 2.25 (s, 3H), 2.40-2.45 (t, 2H), 2.70-2.80 (m, 2H), 3.70 (s, 3H), 4.05 (t, 2H), 5.15 (m, 2H), 6.85-7.00 (m, 6H), 7.30-7.45 (m, 3H), 7.50 (s, 1H), 7.55 (d, 1H).

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenoxy)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**2c**): (oil) ^{1}H NMR ($CDCl_3$) δ 1.30-1.40 (m, 1H), 1.40-1.55 (m, 1H), 2.10-2.20 (m, 2H), 2.25 (s, 3H), 2.40 (t, 2H), 2.70-2.75 (m, 2H), 3.70 (s, 3H), 4.00 (t, 2H), 5.15 (m, 2H), 6.40-6.55 (m, 3H), 7.00 (t, 2H), 7.20 (t, 1H), 7.35 (d, 1H), 7.40 (dd, 2H), 7.50 (s, 1H), 7.55 (d, 1H).

(*S*)-1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile (**2d**): LC/MS (m/z) 482 (MH^+), Rt = 4.24, purity: 84 %.

1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran (**2e**): LC/MS (m/z) 439 (MH^+), Rt = 4.33, purity: 77 %.

(*S*)-1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2f**): LC/MS (m/z) 468 (MH^+), Rt = 4.11, purity: >99 %.

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran (**2g**): LC/MS (m/z) 425 (MH^+), Rt = 4.15, purity: >99 %.

5-[3-[[3-(1-Phenyl-1,3-dihydroisobenzofuran-1-yl)propyl]methylamino]propyl]-1,4-benzodioxane (**2h**): LC/MS (m/z) 444 (MH^+), Rt = 4.12, purity: 97 %.

5-[3-[[3-[1-(3-Chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane (**2i**): LC/MS (m/z) 478 (MH^+), Rt = 4.45, purity: 93 %.

5-[3-[[3-[1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane (**2j**): LC/MS (m/z) 462 (MH^+), Rt = 4.21, purity: 93 %.

5-[3-[[3-[1-(3-Trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane (**2k**): LC/MS (m/z) 512 (MH^+), Rt = 4.59, purity: 90 %.

1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2l**): LC/MS (m/z) 503 (MH^+), Rt = 4.59, purity: >99 %.

1-[3-[4-(1*H*-Indol-4-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2m**): LC/MS (m/z) 481 (MH^+), Rt = 5.61, purity: 97 %.

1-[3-[4-(1*H*-Indol-5-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2n**): LC/MS (m/z) 481 (MH^+), Rt = 5.69, purity: 94 %.

1-[3-[4-(6-chloro-1*H*-Indol-3-yl)piperidinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**2o**): LC/MS (m/z) 514 (MH^+), Rt = 6.38, purity: 96 %.

Example 3

5-[3-[[3-[-5-Fluoro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane oxalate (3). A solution of 3-(1,4-benzodioxan-5-yl)propionic acid (0.8 g, 3.8 mmol), thionyl chloride (1 mL, 13.7 mmol) and one droplet of N,N-dimethylformamide in dichloromethane (30 mL) was boiled under reflux for 2 h. The volatile solvents were evaporated *in vacuo* and the remaining oil was

dissolved in dichloromethane (30 mL). The resulting solution was added to a solution [3-[-5-fluoro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamine (3.0 g, 10 mmol) and triethylamine (10 mL) in dichloromethane (100 mL). After stirring for 16 h the volatile solvents were evaporated *in vacuo* and the remaining oil was purified by column chromatography (ethyl acetate/heptane 75:25) affording 1.4 g of crude amide which was used without further purification.

To a solution of the amide (1.4 g, 2.8 mmol) in tetrahydrofuran (200 mL) was added lithium aluminum hydride (1.0 g, 2.6 mmol). After boiling of the resulting mixture under reflux for 3 h, the reaction mixture was cooled to 0 °C and carefully treated with water (1 mL) and 4 N aqueous sodium hydroxide (1 mL). The resulting mixture was filtered and dried (Na_2SO_4). Evaporation of the volatile solvents afforded the title compound as an oil which was precipitated as its oxalate in acetone 0.9 g (19%): mp 131-33 °C; ^{1}H NMR (DMSO-d_6) δ 1.35-1.45 (m, 1H), 1.45-1.55 (m, 1H), 1.75-1.80 (m, 2H), 2.10-2.25 (m, 2H), 2.50-2.55 (m, 2H), 2.60 (s, 3H), 2.90 (t, 2H), 2.95 (t, 2H), 4.20-4.25 (m, 4H), 5.10 (m, 2H), 6.65-6.75 (m, 3H), 7.10-7.15 (m, 4H), 7.45-7.60 (m, 3H); MS m/z, 480 (MH+, 100), 225 (34), 109 (51).

Example 4

1-[3-[[2-(1*H*-Indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4a**). To a suspension of acryl ester Wang resin ($CH_2CHC(O)OR'$, HOR' = Wang resin) (loading 1.0 mmol/g) (300 mg, 0.30 mmol) (prepared from Wang resin (Loading 1.09 mmol/g, 200-400 mesh, 1% divinylbenzene) in analogy with the procedure described for the preparation of acryl ester hydroxymethyl polystyrene by Brown et al., J. Am. Chem. Soc., 1997, 119, 3288-95) in N,N-dimethylformamide (1.5 mL) was added a solution of 2-(1*H*-indolyl-3-yl)ethylamine (96 mg, 0.60 mmol) in N,N-dimethylformamide (1.5 mL). After stirring of the resulting suspension at room temperature for 16 h, the resin was filtered off and subsequently washed with 0.3 M diisopropylethylamine in N,N-dimethylformamide (3 X 2.5 mL), methanol (2 X 2.5 mL) and dichloromethane (2 X 2.5 mL).

To a suspension of the resulting resin in acetonitrile (1.5 mL) was added a solution of 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**9**)

(473 mg, 1.5 mmol) in acetonitrile (1.5 mL) and diisopropylethylamine (280 mL, 1.6 mmol). After heating of the resulting mixture at 75 °C under stirring for 16 h, the resin was filtered off. The resin was subsequently washed with acetonitrile (3 X 2.5 mL), methanol (3 X 2.5 mL), and dichloromethane (3 X 2.5 mL). The resin was suspended in N,N-dimethylformamide and diisopropylethylamine (280 mL, 1.6 mmol) and acetic anhydride (140 mL, 1.5 mmol) was added. After stirring of the resulting mixture for 16 h the resin was filtered off and washed with N,N-dimethylformamide (3 X 2.5 mL), methanol (3 X 2.5 mL), and dichloromethane (3 X 2.5 mL).

The intermediate resin was suspended in N,N-dimethylformamide (2 mL) and a solution of iodomethan (187 mL, 3.0 mmol) in N,N-dimethylformamide was added. After stirring of the resulting mixture for 16 h at room temperature, the resin was filtered off and washed with N,N-dimethylformamide (3 X 2.5 mL), methanol (3 X 2.5 mL), and dichloromethane (3 X 2.5 mL). To the resulting resin was added N,N-dimethylformamide (3.0 mL) and Di-isopropylethylamine (165 mL, 0.94 mmol) and the mixture was stirred for 16 h. The resin was filtered off and washed with methanol (2 X 2.0 mL). The cleavage solution and the washing solutions were collected and the solvent evaporated *in vacuo*. The remaining oil was purified by ion exchange chromatography using an 6 mL Varian SCX column (1225-6011). The column was preconditioned with 10% acetic acid in methanol (3 mL) and the crude product was loaded on the column in a 2:1 mixture of methanol and 1-methyl-2-pyrrolidinone (3 mL). After the column was washed with methanol (18 mL) and acetonitrile (3 mL) the product was eluted from the column with 4 N ammonia in methanol (4 mL) and subsequent evaporation of the solvents *in vacuo* afforded 13.9 mg (10%) of the title compound as an oil: LC/MS (m/z) 454 (MH^+), Rt = 6.13 , purity: 98 %.

The following compounds were prepared analogously:

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4b**): LC/MS (m/z) 445 (MH^+), R_t = 8.58 , purity: 88%

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4c**): ^1H NMR ($CDCl_3$) δ 1.30-1.60 (m, 2H), 2.00-2.20 (m, 2H), 2.40-2.55 (m, 2H), 2.55-2.70 (m, 4H), 3.00-3.15 (broad s, 2 H), 3.80 (s, 3H), 5.05-

5.20 (m, 4H), 5.75-5.85 (m, 1H), 6.65-6.80 (m, 3H), 7.00 (t, 2H), 7.20 (t, 1H), 7.30 (d, 1H), 7.40 (m, 2H), 7.50 (s, 1H), 7.60 (d, 1H); LC/MS (m/z) 471 (MH^+), R_t = 8.85 , purity: 91%

1-(4-Fluorophenyl)-1-[3-[[2-(2-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4d**): ^1H NMR ($CDCl_3$) δ 1.25-1.40 (m, 1H), 1.40-1.55 (m, 1H), 2.05-2.25 (m, 2H), 2.40-2.50 (m, 2H), 2.50-2.65 (m, 2H), 2.65-2.75 (m, 2H), 3.00-3.15 (m, 2 H), 3.80 (s, 3H); 5.05-5.20 (m, 4H), 5.75-5.90 (m, 1H), 6.75-6.90 (m, 2H), 6.95-7.10 (m, 3H), 7.20 (t, 1H), 7.30 (d, 1H), 7.35-7.45 (m, 2H), 7.45 (s, 1H), 7.60 (d, 1H); LC/MS (m/z) 471 (MH^+), R_t = 7.82 , purity: >89%

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4e**): LC/MS (m/z) 475 (MH^+), R_t = 8.68 , purity: 94%

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4f**): LC/MS (m/z) 500 (MH^+), R_t = 8.95 , purity: 90%

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4g**): LC/MS (m/z) 431 (MH^+), R_t = 8.58 , purity: 95%

1-[3-[[2-(1*H*-Indolyl-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4h**): LC/MS (m/z) 480 (MH^+), R_t = 8.87 , purity: 93%

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4i**): LC/MS (m/z) 457 (MH^+), R_t = 6.40 , purity:>99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4j**): LC/MS (m/z) 459 (MH^+), R_t = 6.43 , purity:>99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4k**): LC/MS (m/z) 485 (MH^+), R_t = 6.77 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4l**): LC/MS (m/z) 485 (MH^+), R_t = 6.63 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4m**): LC/MS (m/z) 475 (MH^+), R_t = 6.20 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4n**): LC/MS (m/z) 501 (MH^+), R_t = 6.50 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4o**): LC/MS (m/z) 475 (MH^+), R_t = 6.35 , purity: >99%

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile (**4p**): LC/MS (m/z) 501 (MH^+), R_t = 6.65 , purity: >99%

1-[3-[(2-Benzyloxyethyl)methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4q**): LC/MS (m/z) 445 (MH^+), R_t = 6.18 , purity: 98%

1-[3-[(2-Benzyloxyethyl)(prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4r**): LC/MS (m/z) 471 (MH^+), R_t = 6.55 , purity: 97%

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4s**): LC/MS (m/z) 468 (MH^+), R_t = 6.28 , purity:80%

1-[3-[[3-(1*H*-Indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4t**): LC/MS (m/z) 494 (MH^+), R_t = 6.60 , purity:82%

1-[3-[[3-(1*H*-Indol-3-yl)propyl](prop-2-yn-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4u**): LC/MS (m/z) 492 (MH^+), R_t = 6.59 , purity:73%

Example 5

5-hydroxymethyl-1,4-benzodioxan (**5**). To a suspension of lithium aluminum hydride (7.0 g, 0.18 mol) in dry diethyl ether (100 mL) was added a solution of ethyl 1,4-benzodioxan-5-carboxylate (35 g, 0.17 mol) in diethyl ether (100 mL). After boiling under reflux for 2 h, the reaction mixture was cooled to 0 °C and carefully treated with water (35 mL) and 4 N aqueous sodium hydroxide (35 mL). The resulting mixture was filtered and dried (Na_2SO_4). Evaporation of the solvents afforded 25 g (88%) crystalline title compound: mp 51-53 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 1H), 4.20-4.3 (m, 4H), 4.60 (s, 2H), 6.75-6.90 (m, 3H).

Example 6

2-(1,4-benzodioxan-5-yl)acetic acid (**6**). To a solution of 5-hydroxymethyl-1,4-benzodioxan (8.0 g, 48 mmol) in dichloromethane (200 mL) was added two droplets of N,N-dimethylformamide and thionyl chloride (5.0 mL, 68 mmol) at room temperature. After the resulting solution was boiled under reflux for 1 h and subsequently cooled to room temperature water (100 mL) was added. The phases were separated and the organic phase was dried ($MgSO_4$) and the solvents evaporated *in vacuo*. A solution of the remaining oil (8.5 g, 46 mmol) was added to a mixture of sodium cyanide (5.0 g, 102 mmol) and N,N-dimethylformamide (100 mL) at room temperature. After stirring for 16 h at room temperature ice was added and the resulting slurry was extracted with diethyl ether (2 X 250 mL). The collected organic phases were washed with saturated calcium chloride, dried (Na_2SO_4) and the solvents were evaporated *in vacuo*. A mixture of the remaining oil (6.0 g, 34 mmol), ethanol (200 mL), sodium hydroxide (6.0 g) and water (6 mL) was

boiled under reflux for 16 h. After evaporation of the solvents *in vacuo*, water (200 mL) was added and the resulting slurry was extracted with diethyl ether (2 X 200 mL). The collected organic phases were washed with brine, dried (Na_2SO_4) and the solvents were evaporated *in vacuo* affording 4.0 g (43%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 2H), 4.15-4.30 (m, 4H), 6.70-6.85 (m, 3H).

Example 7

5-(2-bromoethyl)-1,4-benzodioxan (**7a**). To a solution of 2-(1,4-benzodioxan-5-yl)acetic acid (**6**) (4.0 g, 21 mmol) in tetrahydrofuran (200 mL) was added lithium aluminum hydride (1.0 g, 26 mmol). After boiling under reflux for 2 h the reaction mixture was cooled to 0 °C and carefully treated with water (1 mL) and 4 N aqueous sodium hydroxide (1 mL). The resulting mixture was filtered and dried (Na_2SO_4). Evaporation of the solvents afforded crude intermediate alcohol (3.9 g, 21 mmol) as an oil which was used without further purification. To a solution of the intermediate alcohol and tetrabromomethane (8.8 g, 27 mmol) in acetonitrile (120 mL) was added triphenylphosphine (6.3 g, 24.9 mmol) in small portions at 0 °C. After reaction for further 15 minutes at 0 °C the solvents were evaporated *in vacuo* and the remaining oil was purified by column chromatography (ethyl acetate/heptane 66:34) affording 5.5 g (99%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 3.15 (t, 2H), 3.55 (t, 2H), 4.20-4.35 (m, 4H), 6.65-6.85 (m, 3H).

The following compounds were prepared analogously:

5-(3-Bromopropyl)-1,4-benzodioxan (**7b**): (oil) ^{1}H NMR ($CDCl_3$) δ 2.15 (qui, 2H), 2.75 (t, 2H), 3.40 (t, 2H), 4.20-4.30 (m, 4H), 6.65-6.75 (m, 3H).

5-(4-Bromobutyl)-1,4-benzodioxan (**7c**): (oil) ^{1}H NMR ($CDCl_3$) δ 1.70-1.80 (qui, 2H), 1.85-1.90 (qui, 2H), 2.60 (t, 2H), 3.40 (t, 2H), 4.25 (m, 4H), 6.65-6.75 (m, 3H).

1-(2-Bromoethoxy)-2-methoxybenzene (**7d**): (oil) ^{1}H NMR ($CDCl_3$) δ 3.65 (t, 2H), 3.85 (s, 3H), 4.30 (t, 2H), 6.80-7.05 (m, 4H).

1-(2-Bromoethoxy)-3-methoxybenzene (**7e**): (oil) ^{1}H NMR ($CDCl_3$) δ 3.60 (t, 2H), 3.80 (s, 3H), 4.25 (t, 2H), 6.45-6.55 (m, 3H), 7.15 (t, 1H).

Example 8

4-(1,4-Benzodioxan-5-yl)butanoic acid (**8a**). Neat 5-(4-bromoethyl)-1,4-benzodioxan (**7c**) (18.0 g, 74 mmol) was added to a mixture of diethyl malonate (12 g, 75 mmol), potassium tert-butoxide (8.4 g, 75 mmol), toluene (250 mL) and dimethyl sulfoxide (50 mL) at room temperature. The resulting mixture was heated at 50 °C for 3 h, cooled to room temperature and water was added. After the slurry was acidified with concentrated hydrochloric acid the phases were separated. The organic phase was dried (Na_2SO_4) and the solvents evaporated *in vacuo*. The remaining oil was dissolved in ethanol (200 mL) and 9 N aqueous sodium hydroxide. After boiling of the resulting mixture under reflux for 15 minutes the solution was stirred at room temperature for 1 h. The solvents were evaporated and the remaining oil was diluted in water (200 mL) and extracted with diethyl ether (2 X 100 mL). The aqueous phase was acidified with 4 N hydrochloric acid and extracted with ethyl acetate (2 X 200 mL). Drying of the collected organic phases and evaporation of the solvents *in vacuo* afforded the intermediate dicarboxylic acid as an oil (5.0 g). The crude oil was diluted in pyridine (10 mL) and the resulting solution was heated at 115 °C for 1 h. After cooling to room temperature, water (50 mL) was added and the aqueous phase was acidified with 4 N hydrochloric acid. The resulting slurry was extracted with diethyl ether (2 X 50 mL) and the collected organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* afforded 3.8 g (23%) of the title compound as an oil.

The following compound was prepared analogously:

3-(1,4-Benzodioxan-5-yl)propionic acid (**8b**): (oil) ^{1}H NMR ($CDCl_3$) δ 2.65 (t, 2H), 2.95 (t, 2H), 4.20-4.30 (m, 4H), 6.65-6.80 (m, 3H).

Example 9

1-(3-Chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**9**). To a mixture of 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (43 g, 138 mmol), potassium carbonate (30 g, 217 mmol), and ethanol (400

mL) was added ethyl bromoacetate (20 mL, 180 mmol) at room temperature and the resulting mixture was boiled under reflux for 90 minutes. After cooling to room temperature water (800 mL) and ethyl acetate (500 mL) was added and the phases were separated. The organic phase was washed with brine, dried (Na_2SO_4) and the solvents evaporated *in vacuo*. The remaining oil (36 g, 101 mmol) was added slowly to a mixture of ethyl chloroformate (50 mL, 523 mmol), potassium carbonate (36 g, 260) and toluene (300 mL) at 90 °C. After boiling of the resulting mixture under reflux for 1 h and cooling to room temperature, the solvents were evaporated *in vacuo*. The remaining oil was purified by column chromatography (ethyl acetate/heptane 1:3) giving 15 g (34%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 1.60-1.90 (m, 2H), 2.20-2.45 (m, 2H), 3.45-3.55 (m, 2H), 5.20 (m, 2H), 6.95-7.10 (t, 2H), 7.40-7.55 (m, 4H), 7.60 (d, 1H).

Example 10

[2-(2-Methoxyphenoxy)ethyl]methylamine (**10a**). A solution of 1-(2-bromoethoxy)-2-methoxybenzene (**7d**) (7.7 g, 33 mmol) in a 33% solution of methylamine in ethanol was heated at 80 °C in a sealed tube for 16 h. After cooling to room temperature, the solvents were evaporated *in vacuo*. A 2 N aqueous solution of sodium hydroxide was added to the remaining oil and the resulting slurry was extracted with ethyl acetate (2 X 250 mL). The collected organic phases were dried (Na_2SO_4) and the solvents evaporated *in vacuo* giving 5.9 g (98%) of the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 1.85 (broad s, 1H), 2.50 (s, 3H), 3.00 (t, 2H), 3.85 (s, 3H), 4.10 (t, 2H), 6.85-6.95 (m, 4H).

The following compound was prepared analogously:

[2-(3-Methoxyphenoxy)ethyl]methylamine (**10b**): (oil) ^{1}H NMR ($CDCl_3$) δ 1.85 (broad s, 1H), 2.50 (s, 3H), 2.95 (t, 2H), 3.80 (s, 3H), 4.05 (t, 2H), 6.45-6.55 (m, 3H), 7.15 (t, 1H).

Example 11

2-(4-Chlorobutyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11a**). A 2 L round bottom flask was charged with 2,2-dimethyldioxolan-4-ylmethoxymethyl polystyrene (90 g, 72 mmol, commercially available as (±)-1-(2,3-isopropylidene) glycerol polystyrene from Calbiochem-Novabiochem, cat. no. 01-64-0291). Toluene (900 mL) followed by p-

toluenesulfonic acid mono hydrate (5.0 g, 26 mmol), sodium sulfate (25 g), and readily available 5-chloropentanal (25.5 g, 211 mmol) were added and the mixture heated at reflux for 12 h. The reflux condenser was replaced by a Dean-Stark apparatus and the mixture was heated at reflux for an additional 3 h. After cooling of the reaction mixture to 60 °C, the resin was filtered and washed with toluene (200 mL), tetrahydrofuran/pyridine (1:1, 200 mL), tetrahydrofuran/water/pyridine (10:10:1, 200 mL), methanol (200 mL), water (200 mL), tetrahydrofuran (200 mL), dichloromethane (200 mL), methanol (3 X 200 mL), and dichloromethane (3 X 200 mL). The resin was dried *in vacuo* (55 °C, 12 h) to yield the title compound **11a** (97 g).

The following compounds were prepared analogously:

2-(3-Chloropropyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11b**)

2-(5-Chloropentyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11c**)

Example 12

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**4s**). 2-(4-Chlorobutyl)-dioxolan-4-ylmethoxymethyl polystyrene (**11a**) (8.0 g, 6.1 mmol) was suspended in dry N,N-dimethylformamide (90 mL). Sodium iodide (3.38 g, 22.5 mmol) was added followed by diisopropylethylamine (6.30 mL, 36 mmol) and 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (5.56 g, 18 mmol). The reaction mixture was heated at 80 °C under stirring for 12 h. After cooling to room temperature, the resin was filtered and washed with with N,N-dimethylformamide (3 X 65 mL), methanol (3 X 60 mL), tetrahydrofuran (3 X 60 mL), and then subsequently with methanol and tetrahydrofuran (each approximately 40 mL, 5 cycles). Finally, the resin was washed with tetrahydrofuran (4 X 40 mL) and dried *in vacuo* (55 °C, 12 h, 9.5 g).

An aliquot of this material (147 mg, 0.112 mmol) and phenylhydrazine hydrochloride (43 mg, 0.297 mmol) were mixed in a reactor tube. A 0.5 M solution of anhydrous zinc chloride in acetic acid (1.5 mL) was added and the reaction tube was sealed. The reaction mixture was stirred for 12 h at 75 °C. After cooling to room temperature, the reaction mixture was filtered and the residual resin washed with dimethylsulfoxide (1.5 mL). To the combined filtrates was added saturated aqueous sodium bicarbonate solution (1.5 mL). The

solution was loaded on a reversed solid phase extraction column (C-18, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220508), pre-conditioned with methanol (3 mL) and water (3 mL). The column was washed with water (4 mL) and the product was eluted with methanol (4.5 mL). The resulting solution was loaded on an ion exchange column (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220776), pre-conditioned with 10 % solution of acetic acid in methanol (3 mL) and the column was washed with methanol (4 mL) and acetonitrile (4 mL), followed by elution with 4 N solution of ammonia in methanol (4.5 mL). Evaporation of the volatile solvents afforded the title compound (**4s**) as a colourless oil (22 mg, 42 %). LC/MS (m/z) 468 (MH^+), Rt = 4.30, purity: 83 %.

The following compounds were prepared analogously:

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12a**): LC/MS (m/z) 468 (MH^+), Rt = 4.22, purity: 96 %.

1-[3-[[2-(7-Fluoro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12b**): ^1H NMR ($CDCl_3$) δ 1.2-1.4 (m, 1H), 1.4-1.55 (m,1H), 2.0-2.25 (m, 2H), 2.25 (s, 3H), 2.39 (t, 2H), 2.60 (t, 2H), 2.86 (t, 2H), 5.05-5.21 (m, 2H), 6.93-7.07 (m, 4H), 7.17-7.3 (m, 2H), 7.3-7.4 (m, 3H), 7.4-7.5 (m, 1H), 7.5-7.6 (m, 1H); LC/MS (m/z) 472 (MH^+), Rt = 4.12, purity: 86 %.

5-Fluoro-1-[3-[[3-(5-methyl–1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran (**12c**): LC/MS (m/z) 475 (MH^+), Rt = 4.57, purity: 92 %.

5-Fluoro-1-[3-[[3-(7-fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran (**12d**): LC/MS (m/z) 479 (MH^+), Rt = 4.47, purity: 94 %.

1-[3-[[3-(5-Methyl –1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12e**): LC/MS (m/z) 482 (MH^+), Rt = 4.54, purity: 80 %.

1-[3-[Ethyl[3-(1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12f**): LC/MS (m/z) 482 (MH^+), Rt = 4.31, purity: 94 %.

1-[3-[Ethyl[2-(5-methyl –1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12g**): LC/MS (m/z) 482 (MH^+), Rt = 4.38, purity: 89 %.

1-[3-[[3-(7-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12h**): LC/MS (m/z) 486 (MH^+), Rt = 4.16, purity: 79 %.

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12i**): ^1H NMR ($CDCl_3$) δ 1.23-1.39 (m, 1H), 1.39-1.54 (m, 1H), 1.80 (tt, 2H), 2.06-2.24 (m, 5H), 2.30 (t, 2H), 2.34 (t, 2H), 2.68 (t, 2H), 5.13 (d, 1H), 5.17 (d, 1H), 6.93 (dt, 2H), 6.99 (t, 2H), 7.21 (dd, 1H), 7.23-7.29 (m, 1H), 7.33 (d, 1H), 7.40 (dd, 2H), 7.47 (s, 1H), 7.55 (d, 1H), 8.01 (s, 1H); LC/MS (m/z) 486 (MH^+), Rt = 4.12, purity: 98 %.

1-[3-[Ethyl[2-(5-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12j**): ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H), 1.25-1.38 (m, 1H), 1.42-1.54 (m, 1H), 2.10 (ddd, 1H), 2.18 (ddd, 1H), 2.49 (t, 2H), 2.56 (q, 2H), 2.61-2.70 (m, 2H), 2.74-2.82 (m, 2H), 5.13 (d, 1H), 5.18 (d, 1H), 6.94 (dt, 2H), 6.99 (t, 2H), 7.19 (dd, 1H), 7.23-7.30 (m, 2H), 7.38 (dd, 2H), 7.47 (s, 1H), 7.54 (d, 1H), 8.01 (s, 1H); LC/MS (m/z) 486 (MH^+), Rt = 4.24, purity: 95 %.

1-[3-[Ethyl[2-(7-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12k**): ^1H NMR ($CDCl_3$) δ 1.02 (t, 3H), 1.22-1.37 (m, 1H), 1.42-1.53 (m,1H), 2.0-2.2 (m, 2H), 2.36-2.6 (m, 4H), 2.67 (t, 2H), 2.81 (t, 2H), 5.12 (dd, 1H), 5.16 (d, 1H), 6.86-7.06 (m, 4H), 7.2-7.4 (m, 5H), 7.46 (d, 1H), 7.54 (d, 1H); LC/MS (m/z) 486 (MH^+), Rt = 4.26, purity: 91 %.

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12l**): LC/MS (m/z) 488 (MH^+), Rt = 4.30, purity: 85 %.

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl] – 5-fluoro –1-(4-fluorophenyl) –1,3-dihydroisobenzofuran (**12m**): LC/MS (m/z) 495 (MH^+), Rt = 4.64, purity: 94 %.

1-[3-[[4-(5-Methyl–1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12n**): LC/MS (m/z) 496 (MH^+), Rt = 4.50, purity: 78 %.

1-[3-[Ethyl[3-(5-methyl–1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12o**): LC/MS (m/z) 496 (MH^+), Rt = 4.50, purity: 92 %.

1-[3-[Ethyl[3-(7-fluoro–1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12p**): LC/MS (m/z) 500 (MH^+), Rt = 4.39, purity: 91 %.

1-[3-[Ethyl[3-(5-fluoro–1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12q**): ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.21-1.36 (m, 1H), 1.36-1.50 (m, 1H), 1.77 (tt, 2H), 2.10 (ddd, 1H), 2.18 (ddd, 1H), 2.34-2.50 (m, 6H), 2.65 (t, 2H), 5.12 (d, 1H), 5.15 (d, 1H), 6.90-7.04 (m, 4H), 7.20 (dd, 1H), 7.25 (dd, 1H), 7.30 (d, 1H), 7.36 (m, 2H), 7.45 (s, 1H), 7.52 (d, 1H), 8.12 (s, 1H); LC/MS (m/z) 500 (MH^+), Rt = 4.35, purity: 94 %.

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12r**): LC/MS (m/z) 502 (MH^+), Rt = 4.55, purity: 91 %.

1-[3-[[2-(7-Chloro –1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12s**): LC/MS (m/z) 502 (MH^+), Rt = 4.41, purity: 80 %.

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12t**): LC/MS (m/z) 502 (MH^+), Rt = 4.44, purity: 95 %.

1-[3-[[2-(5,7-Difluoro –1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12u**): LC/MS (m/z) 504 (MH^+), Rt = 4.35, purity: 92 %.

1-[3-[[4-(5-Fluoro –1*H*-indol-3-yl)butyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12v**): LC/MS (m/z) 514 (MH^+), Rt = 4.50, purity: 91 %.

1-[3-[[4-(5-Chloro –1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12w**): LC/MS (m/z) 516 (MH^+), Rt = 4.59, purity: 90 %.

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12x**): LC/MS (m/z) 516 (MH^+), Rt = 4.56, purity: 97 %.

1-[3-[[3-(5,7-Difluoro –1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12y**): LC/MS (m/z) 518 (MH^+), Rt = 4.47, purity: 90 %.

1-[3-[[2-(5-Bromo –1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12z**): LC/MS (m/z) 532 (MH^+), Rt = 4.46, purity: 87 %.

1-[3-[[3-(5-Bromo –1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12aa**): LC/MS (m/z) 546 (MH^+), Rt = 4.59, purity: 88 %.

1-[3-[[2-(5-Bromo –1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ab**): LC/MS (m/z) 546 (MH^+), Rt = 4.50, purity: 90 %.

1-[3-[[4-(5-Bromo –1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ac**): LC/MS (m/z) 560 (MH^+), Rt = 4.61, purity: 90 %.

1-[3-[[3-(5-Bromo –1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ad**): LC/MS (m/z) 560 (MH^+), Rt = 4.62, purity: 92 %.

1-[3-[Ethyl[2-(5-iodo –1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ae**): LC/MS (m/z) 594 (MH^+), Rt = 4.60, purity: 82 %.

1-[3-[Ethyl[3-(5-iodo –1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12af**): LC/MS (m/z) 608 (MH^+), Rt = 4.72, purity: 71 %.

1-[2-[[4-(5-Chloro –1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ag**): LC/MS (m/z) 502 (MH^+), Rt = 4.50, purity: 90 %.

1-[2-[[4-(5-Bromo –1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ah**): LC/MS (m/z) 546 (MH^+), Rt = 4.55, purity: 83 %.

1-[4-[[2-(5,7-Difluoro –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ai**): LC/MS (m/z) 504 (MH^+), Rt = 4.36, purity: 87 %.

1-[4-[[2-(7-Chloro –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12aj**): LC/MS (m/z) 502 (MH^+), Rt = 4.42, purity: 70 %.

1-[4-[[2-(5-Chloro –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ak**): LC/MS (m/z) 502 (MH^+), Rt = 4.45, purity: 91 %.

1-[4-[[2-(5-Bromo –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12al**): LC/MS (m/z) 546 (MH^+), Rt = 4.48, purity: 90 %.

1-[4-[[2-(5-Methyl –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12am**): LC/MS (m/z) 482 (MH^+), Rt = 4.37, purity: 87 %.

1-[4-[[2-(5-Iodo –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12an**): LC/MS (m/z) 594 (MH^+), Rt = 4.57, purity: 83 %.

1-[4-[[2-(5-(2-methyl-2-propyl)–1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ao**): LC/MS (m/z) 524 (MH^+), Rt = 4.85, purity: 91 %.

1-[4-[[2-(5-(2-Propyl) –1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**12ap**): LC/MS (m/z) 510 (MH^+), Rt = 4.72, purity: 92 %.

Example 13

1-[3-[[2-(5-Methyl –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13a**).

2-(3-Chloropropyl)-1,3-dioxolan-4-ylmethoxymethyl polystyrene (2.0 g, 1.6 mmol) was suspended in dry N,N-dimethylformamide (15 mL). Sodium iodide (0.67 g, 4.5 mmol) was added followed by diisopropylethylamine (1.70 mL, 9.6 mmol) and allyl amine (0.28 g, 4.8 mmol). The reaction mixture was heated at 80 °C under stirring for 12 h. After cooling to room temperature, the resin was filtered and washed with N,N-dimethylformamide (3 X 15 mL), methanol (3 X 15 mL), tetrahydrofuran (3 X 15 mL), and subsequently with methanol and tetrahydrofuran (each 10 mL, 5 cycles). Finally, the resin was washed with tetrahydrofuran (4 X 10 mL) and dried *in vacuo* (55 °C, 12 h). The resin was then suspended in dry N,N-dimethylformamide (20 mL). Sodium iodide (0.60 g, 4.0 mmol) was added followed by diisopropylethylamine (0.48 mL, 2.7 mmol) and 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**9**) (0.79 g, 2.5 mmol). The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the resin was filtered and washed with with N,N-dimethylformamide (3 X 15 mL), methanol (3 X 15 mL), tetrahydrofuran (3 X 15 mL), and then subsequently with methanol and tetrahydrofuran (each ca. 15 mL, 5 cycles). Finally, the resin was washed with tetrahydrofuran (4 X 15 mL) and dried *in vacuo* (55 °C, 12 h, 2.1 g).

An aliquot of this material (120 mg, ca. 0.08 mmol) and 4-methylphenylhydrazine hydrochloride (ca. 40 mg, 0.20 mmol) were mixed in a reactor tube. A 0.5 M solution of anhydrous zinc chloride in acetic acid (1.5 mL) was added and the reaction tube was sealed. The reaction mixture was stirred for 12 h at 75 °C. After cooling to room temperature, the reaction mixture was filtered and the residual resin washed with dimethylsulfoxide (1.5 mL). To the combined filtrates was added saturated aqueous sodium bicarbonate solution (1.5 mL). The solution was loaded on a reversed phase column (C-18, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220508), pre-conditioned with methanol (3 mL) and water (3 mL). The column was washed with water

(4 mL) and the product was eluted with methanol (4.5 mL). After evaporation of the volatile solvents, the crude product was purified by preparative reversed phase HPLC chromatography. The resulting solution was loaded on an ion exchange column (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220776), pre-conditioned with 10 % solution of acetic acid in methanol (3 mL) and the column was washed with methanol (4 mL) and acetonitrile (4 mL), followed by elution with 4 N solution of ammonia in methanol (4.5 mL). Evaporation of the volatile solvents afforded the title compound (**13a**) as a colorless oil (2 mg, 4 μmol, 5 %). LC/MS (m/z) 494 (MH^+), Rt = 4.44, purity: 93 %.

The following compounds were prepared analogously:

1-[3-[[2-(5-Fluoro –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13b**): LC/MS (m/z) 498 (MH^+), Rt = 4.31, purity: 96 %.

1-[3-[[2-(7-Fluoro –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13c**): LC/MS (m/z) 498 (MH^+), Rt = 4.34, purity: 86 %.

1-[3-[[3-(5-Fluoro –1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13d**): LC/MS (m/z) 512 (MH^+), Rt = 4.48, purity: 96 %.

1-[3-[[3-(7-Fluoro –1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13e**): LC/MS (m/z) 512 (MH^+), Rt = 4.49, purity: 78 %.

1-[3-[[2-(5-Chloro –1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13f**): LC/MS (m/z) 514 (MH^+), Rt = 4.52, purity: 86 %.

1-[3-[[2-(5,7-Difluoro –1*H*-indol-3-yl)ethyl]propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13g**): LC/MS (m/z) 518 (MH^+), Rt = 4.47, purity: 89 %.

1-[3-[[2-[5-(2-Propyl)-1*H*-indol-3-yl]ethyl](2-propyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13h**): LC/MS (m/z) 524 (MH^+), Rt = 4.78, purity: 96 %.

1-[3-[[3-(4-Fluoro-7-methyl-1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13i**): LC/MS (m/z) 526 (MH^+), Rt = 4.65, purity: 83 %.

1-[3-[[2-(4-Chloro-7-methyl-1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13j**): LC/MS (m/z) 528 (MH^+), Rt = 4.67, purity: 79 %.

1-[3-[[3-(5-Chloro –1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13k**): LC/MS (m/z) 528 (MH^+), Rt = 4.63, purity: 78 %.

1-[3-[[2-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13l**): LC/MS (m/z) 531 (MH^+), Rt = 3.43, purity: 91 %.

1-[3-[[3-(7-Fluoro –1*H*-indol-3-yl)propyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13m**): LC/MS (m/z) 552 (MH^+), Rt = 4.58, purity: 82 %.

1-[3-[[4-(7-Carboxy-1*H*-indol-3-yl)butyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13n**): LC/MS (m/z) 552 (MH^+), Rt = 4.17, purity: 69 %.

1-[3-[[2-[5-Bromo-1*H*-indol-3-yl]ethyl]-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13o**): LC/MS (m/z) 560 (MH^+), Rt = 4.62, purity: 96 %.

1-[3-[[3-(1*H*-Indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13p**): LC/MS (m/z) 574 (MH^+), Rt = 4.78, purity: 93 %.

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13q**): LC/MS (m/z) 574 (MH^+), Rt = 4.82, purity: 93 %.

1-[3-[[2-(5-Fluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13r**): LC/MS (m/z) 578 (MH^+), Rt = 4.71, purity: 95 %.

1-[3-[[3-(1*H*-Pyrrolo[3,2-*h*]quinolin-3-yl)propyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13s**): LC/MS (m/z) 585 (MH^+), Rt = 3.60, purity: 90 %.

1-[3-[[3-(5-Methyl-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13t**): LC/MS (m/z) 588 (MH^+), Rt = 4.96, purity: 82 %.

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13u**): LC/MS (m/z) 592 (MH^+), Rt = 4.82, purity: 90 %.

1-[3-[[2-(5,7-Difluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13v**): LC/MS (m/z) 596 (MH^+), Rt = 4.84, purity: 92 %.

1-[3-[[4-(1*H*-Pyrrolo[3,2-*h*]quinolin-3-yl)butyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13w**): LC/MS (m/z) 599 (MH^+), Rt = 3.71, purity: 83 %.

1-[3-[(2-Phenoxyethyl)[2-[5-(2-propyl)-1*H*-indol-3-yl]ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13x**): LC/MS (m/z) 602 (MH^+), Rt = 5.24, purity: 78 %.

1-[3-[[2-(5-Bromo-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**13y**): LC/MS (m/z) 638 (MH^+), Rt = 4.98, purity: 91 %.

Example 14

1-(3-Iodopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**14a**). A solution/suspension of 1-(3-chloropropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (20 g, 35 mmol, 80 % pure) and sodium iodide (285 g, 1.9 mol) in dry acetone (200 ml) was heated at reflux for 24 h. The mixture was evaporated, and partitioned between ether and water. The ether layer was separated, and was washed successively with water and brine. The organic extract was dried over anhydrous magnesium sulfate, filtered and evaporated to give 1-(3-iodopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (25,8 g, 99 %, 80 % pure) as a thick oil. ^1H NMR ($CDCl_3$) δ 1.6-1.9 (m, 2H),

2.21 (ddd, 1H), 2.31 (ddd, 1H), 3.16 (td, 2H), 5.12 (dt, 1H), 5.21 (dt, 1H), 7.02 (t, 2H), 7.41 (d, 2H), 7.43 (d, 1H), 7.51 (s, 1H), 7.62 (dq, 1H)

The following compounds were prepared analogously:

1-(2-Iodoethyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**14b**): yellow oil, ^{1}H NMR ($CDCl_3$) δ 2.4-2.9 (m, 2H), 3.38 (dt, 1H), 3.46 (dt, 1H), 5.15 (d, 1H), 5.21 (d, 1H), 7.03 (t, 2H), 7.35-7.48 (m, 3H), 7.52 (s, 1H), 7.62 (d, 1H).

1-(4-Iodobutyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**14c**): yellow oil, ^{1}H NMR ($CDCl_3$) δ 1.1-1.5 (m, 2H), 1.81 (tt, 2H), 2.00-2.30 (m, 2H), 3.11 (t, 2H), 5.14 (d, 1H), 5.20 (d, 1H), 7.01 (t, 2H), 7.35-7.47 (m, 3H), 7.51 (s, 1H), 7.60 (d, 1H).

Example 15

1-(3-(Ethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**15a**). To a stirred solution of 1-(3-iodopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (12.9 g, 30 mmol, 8 % pure) in ethanol (150 mL) was added a solution of ethylamine (20.3 g, 450 mmol) in THF (50 mL) portionwise, and the mixture was stirred over night. The solution was evaporated, and was dissolved/suspended in water. The pH was adjusted to 12 using aqueous sodium hydroxide solution (2 M) and was extracted with ether. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to give an oil. This oil was purified by silica chromatography using 50% v/v ethyl acetate/heptane as eluent, followed by 10% v/v triethylamine/ 40% v/v ethyl acetate/heptane followed by 20% v/v triethylamine/ethyl acetate to give the title compound (5.52 g, 57%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3 H), 1.2-1.6 (m, 2H), 2.15 (ddd, 1H), 2.24 (ddd, 1H), 2.57 (q, 2H) 2.58 (t, 2H), 5.12 (dt, 1H), 5.20 (dt, 1H), 7.00 (t, 2H), 7.38 (d, 1H), 7.42 (dd, 2H), 7.49 (s, 1H), 7.58 (ddt, 1H).

The following compounds were prepared analogously:

1-(2-(Methylamino)ethyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**15b**): yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.33-2.72 (m, 4H), 5.13 (d, 1H), 5.20 (d, 1H), 7.01 (t, 2H), 7.37-7.47 (m, 3H), 7.50 (s, 1H), 7.59 (d, 1H).

1-(4-(Methylamino)butyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**15c**): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.00-1.45 (m, 2H), 1.46 (tt, 2H), 2.10 (ddd, 1H), 2.21 (ddd, 1H), 2.37 (s, 3H), 2.50 (t, 2H), 5.13 (d, 1H), 5.19 (d, 1H), 7.00 (t, 2H), 7.34-7.46 (m, 3H), 7.49 (s, 1H), 7.59 (d, 1H).

Pharmacological Testing

The affinity of the compounds of the invention to 5-HT_{1A} receptors was determined by measuring the inhibition of binding of a radioactive ligand at 5-HT_{1A} receptors as described in the following test:

Inhibition of ^{3}H-5-CT Binding to Human 5-HT_{1A} Receptors

By this method the inhibition by drugs of the binding of the 5-HT_{1A} agonist ^{3}H-5-carboxamido tryptamine (^{3}H-5-CT) to cloned human 5-HT_{1A} receptors stably expressed in transfected HeLa cells (HA7) (Fargin, A. *et al*, *J. Biol. Chem.*, **1989**, *264*, 14848) is determined *in vitro*. The assay was performed as a modification of the method described by Harrington, M.A. *et al*, *J. Pharmacol. Exp. Ther.*, **1994**, *268*, 1098. Human 5-HT_{1A} receptors (40 µg of cell homogenate) were incubated for 15 minutes at 37 °C in 50 mM Tris buffer at pH 7.7 in the presence of ^{3}H-5-CT. Non-specific binding was determined by including 10 µM of metergoline. The reaction was terminated by rapid filtration through Unifilter GF/B filters on a Tomtec Cell Harvester. Filters were counted in a Packard Top Counter. The results obtained are presented in table 1 below.

The compounds of the invention have also been tested for their effect on re-uptake of serotonin in the following test:

Inhibition of ^{3}H-5-HT Uptake Into Rat Brain Synaptosomes

Using this method, the ability of drugs to inhibit the accumulation of ^{3}H-5-HT into whole rat brain synaptosomes is determined *in vitro*. The assay was performed as described by Hyttel, J., *Psychopharmacology* **1978**, *60*, 13. The results obtained are presented in table 1:

Table 1

Compound No.	Inhibition of ^{3}H-5-CT binding IC_{50} (nM) % inhibition at 100 nM	Inhibition of serotonin reuptake IC_{50} (nM) % inhibition at 100 nM
1a	39	60
1b	12	13
1c	53	85
2a	1.0	340
2b	6.4	40
2e	38	15
2f	8.6	14
2g	40	20
2j	41	9.7
2m	4.7	Not tested
2n	15	Not tested
2o	12	31
4a	23	54
4b	63	59% inh. at 100 nM
4c	11	4% inh. at 100 nM
4d	4.5	7% inh. at 100 nM

4e	17	160
4f	1.6	4% inh. at 100 nM
4g	18	28% inh. at 100 nM
4h	3.2	69
4i	1.9	26% inh. at 100 nM
4j	6.1	78
4k	0.42	100
4l	76% inh. at 100 nM	27% inh. at 100 nM
4m	65% inh. at 100 nM	74% inh. at 100 nM
4n	14	39% inh. at 100 nM
4o	26	73
4p	19	6% inh. at 100 nM
4q	16	60% inh. at 100 nM
4r	11	19% inh. at 100 nM
4s	30	35
4t	69% inh. at 100 nM	73% inh. at 100 nM
4u	58% inh. at 100 nM	44% inh. at 100 nM
12b	43	10
12c	19	17
12d	31	12
12f	4.7	13
12i	27	20
12j	7.9	14
12k	3.6	8.4
12o	6.2	49% inh. at 100 nM
12p	19	11

12q	12	6.3
12r	16	47% inh. at 100 nM
12s	7.7	18
12u	9.0	22
12v	39	12
12x	14	50% inh. at 100 nM
12aa	16	37% inh. at 100 nM
12ab	20	50% inh. at 100 nM
12ad	21	35% inh. at 100 nM
12ae	11	49% inh. at 100 nM
12af	31	38% inh. at 100 nM
13b	7.4	44
13c	9.6	12
13d	15	21
13e	22	27
13f	31	16% inh. at 100 nM
13g	18	49% inh. at 100 nM
13j	16	61% inh. at 100 nM
13k	19	Not tested
13p	23	Not tested
13q	12	Not tested
13r	8.9	Not tested
13t	23	Not tested
13u	22	Not tested
13v	23	Not tested
13x	26	Not tested
Pindolol*	100	
Paroxetine*	-	0.29

Table 1 * reference compounds

Furthermore, the 5-HT_{1A} antagonistic activity of some of the compounds of the invention has been estimated *in vitro* at cloned 5-HT_{1A} receptors stably expressed in transfected HeLa cells (HA7). In this test, 5-HT_{1A} antagonistic activity is estimated by measuring the ability of the compounds to antagonize the 5-HT induced inhibition of forskolin induced cAMP accumulation. The assay was performed as a modification of the method described by Pauwels, P.J. *et al*, *Biochem. Pharmacol.* **1993**, *45*, 375.

As seen from the above, the compounds of the invention show affinity for the 5-HT_{1A} receptor. Furthermore, many of the compounds of the present invention possess valuable activity as serotonin re-uptake inhibitors.

Accordingly, the compounds are considered useful for the treatment of psychiatric and neurological disorders as mentioned previously.

Pharmaceutical formulation

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilisation of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

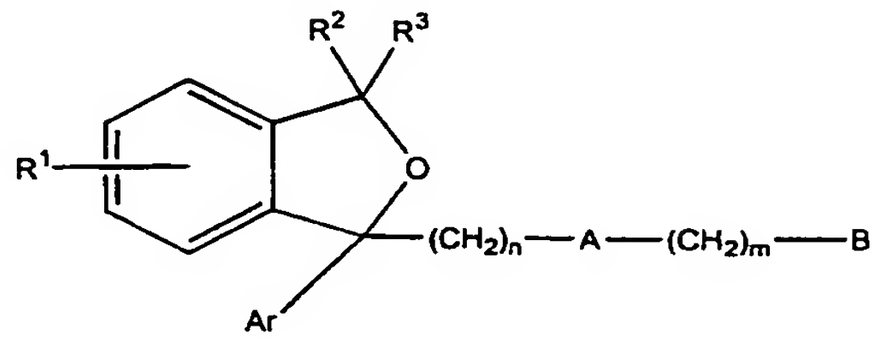
The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of

solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients, or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 1000 mg. The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

Claims:

1. An isobenzofuran having the general Formula I:



(I)

wherein

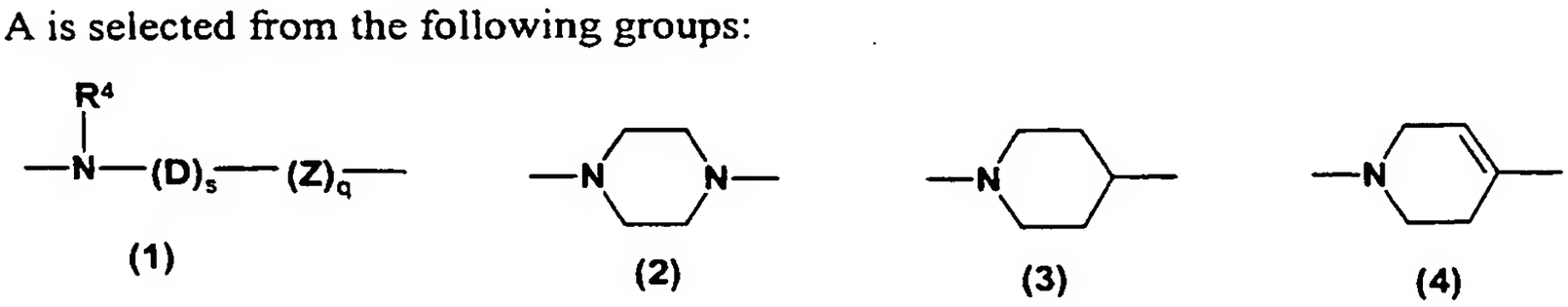
R^1 is hydrogen, halogen, trifluoromethyl, trifluoromethylsulfonyloxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, hydroxy, formyl, acyl, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, acylamino, C_{1-6} alkoxycarbonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, C_{2-12} dialkylaminocarbonylamino, nitro, cyano, COOH, or COO-C_{1-6} alkyl;

R^2 and R^3 are each independently selected from hydrogen, trifluoromethyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl and C_{1-6} alkoxy;

n is 1, 2, 3, 4 or 5;

m is 0 or 1;

A is selected from the following groups:



(1) (2) (3) (4)

wherein

Z is O or S;

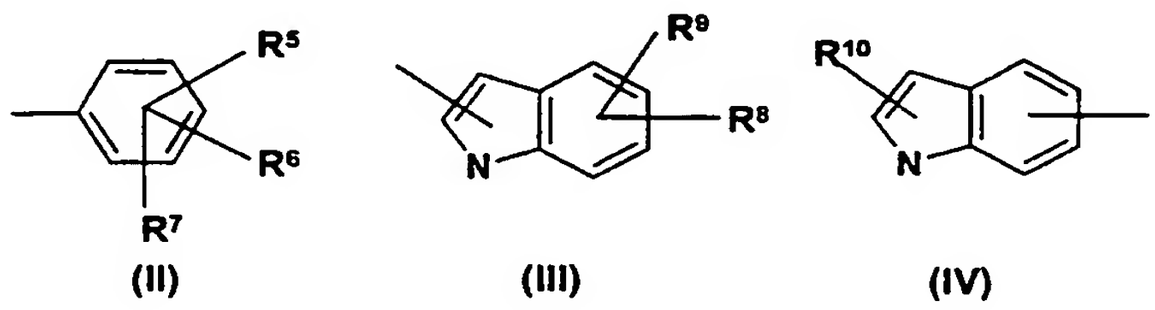
s is 0 or 1;

q is 0 or 1;

R^4 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkyl-Aryl, or C_{1-6}-alkyl-O-Aryl;

D is a spacer group selected from branched or straight chain C_{1-6}-alkylene, C_{2-6}-alkenylene and C_{2-6}-alkynylene;

B is a group selected from a group of formula (II), (III), and (IV)



(II) (III) (IV)

wherein R^5, R^6, R^7, R^8, R^9 and R^{10} are each independently selected among the R^1 substituents;

or R^8 and R^9 together form a fused 5- or 6-membered ring optionally containing further heteroatoms; and the resulting heterocycle is optionally substituted with substituents selected among the R^1 substituents;

or two of the groups of R^5, R^6 and R^7 are linked together thereby forming a $—O—(CH_2)_p—O—$ -bridge wherein p is 1 or 2;

Ar and Aryl are independently selected from the group consisting of phenyl, 2–thienyl, 3–thienyl, 2–furanyl, 3–furanyl, 2–pyrimidyl, 1–indolyl, 2–indolyl, 3–indolyl, 1–indol-2-onyl, 3–indol-2-onyl, 2- or 3–benzofuranyl, 2- or 3–benzothiophenyl, 1–naphthyl or 2–naphthyl, each optionally substituted with halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy, C_{1-6} alkylsulfonyl, cyano, trifluoromethyl, trifluoromethylsulfonyloxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl–C_{1-6} alkyl, nitro, amino, C_{1-6} alkylamino, C_{2-12} dialkylamino, acylamino or alkylenedioxy;

its enantiomers, and pharmaceutically acceptable acid addition salt thereof.

2. A compound of Claim 1, **characterised in** that A is a group of formula (1).

3. A compound of Claim 1, **characterised in** that A is a group of formula (2).

4. A compound of Claim 1, **characterised in** that A is a group of formula (3).

5. A compound of Claim 1, **characterised in** that A is a group of formula (4).

6. A compound of Claim 2, **characterised in** that R^4 is methyl, ethyl, propyl, 2-propen-1-yl, 2-furylmethyl, 2-phenoxyethyl;

7. A compound of any of the Claims 2 and 6, **characterised in** that q = 0;

8. A compound of any of the Claims 2 and 6, **characterised in** that q = 1 and Z is O.

9. A compound of any of the Claims 1 - 8, **characterised in** that B is a group of formula (II).

10. A compound of any of the Claims 1 - 8, **characterised in** that B is a group of formula (III).

11. A compound of any of the Claims 1 - 8, **characterised in** that B is a group of formula (IV).

12. A compound of Claim 9, **characterised in** that at least one of R^5, R^6 and R^7, is methoxy.

13. A compound of Claim 9, **characterised in** that Formula (II) is a benzodioxan group or a 1,2-methylenedioxybenzene group.

14. A compound of Claim 10, **characterised in** that Formula (III) is a 3-indolyl.

15. A compound of Claim 14, **characterised in** that the 3-indolyl is substituted in 5-position by methyl, fluoro, chloro, bromo, iodo, *t*-butyl or *i*-propyl, or in 7-position by fluoro, chloro or carboxy; or disubstituted by 5,7-difluoro, 4-fluoro-7-methyl or 4-chloro-7-methyl or the two substituents together form a pyridyl ring fused to the 3-indolyl.

16. A compound of Claim 11, **characterised in** that Formula (IV) is a 4-indolyl or a 5-indolyl group.

17. A compound of any of the Claims 1 - 16, **characterised in** that Ar is phenyl or phenyl substituted with halogen or CF_3;

18. A compound of Claim 17, **characterised in** that Ar is phenyl which may be substituted with Cl or F in the 4-position or Cl or CF_3 in the 3-position.

19. A compound of any of the Claims 1 - 18, **characterised in** that R^1 is H, CN or F in the 5-position of the isobenzofuran group.

20. A compound of any of the Claims 1 - 19, **characterised in** that R^2 and R^3 are selected from hydrogen or methyl.

21. A compound of any of the Claims 1 - 20, **characterised in** that n = 2, 3 or 4.

22. A compound of claim 21, **characterised in** that n = 3;

23. A compound of any of the Claims 1 - 22, **characterised in** that m = 0.

24. A compound of any of the Claims 1, 18, 19, 20, 21, 22 and 23, **characterised in** that R^2 and R^3 are both hydrogen; R^1 is H, CN or F in the 5-position of the isobenzofuran group; and Ar is phenyl which may be substituted with F or Cl in the 4-position or with Cl or CF_3 in the 3-position.

25. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (1); q = 0; R^4 is methyl; D is propylene; m = 0; and B is a 1,4-benzodioxan group of Formula (II) attached in the 5-position.

26. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (1); R^4 is CH_3 or prop-2-en-1-yl; n = 3; D is ethylene or propylene; and B is a phenyl group wherein at least one substituent is OMe.

27. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (1); q is 0; R^4 is methyl, ethyl, propyl, 2-propen-1-yl, 2-furylmethyl or 2-phenoxyethyl; D is ethylene or propylene; m = 0; and B is a 3-indolyl group of Formula (III).

28. A compound according to claim 27, **characterised in** that the 3-indolyl group is substituted by methyl, fluoro, chloro, bromo, iodo, *t*-butyl or *i*-propyl in the 5-position; or fluoro, chloro or carboxy in the 7-position; or by 5,7-difluoro, 4-fluoro-7-methyl or 4-chloro-7-methyl; or the two substituents together form a pyridyl ring fused to the 3-indolyl-group.

29. A compound of any of the Claims 1 and 24, **characterised in** that A is a group of formula (2) or (3); n = 3; m = 0; and B is an 4- or 5-indolyl-group of Formula (IV) wherein R^{10} is hydrogen; R^1 is CN in the 5-position of the isobenzofuran and Ar is 4-Fluorophenyl.

30. The compound according to claim 1 which is

(-)-1-[3-[[4-(1,4-Benzodioxan-5-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate,

1-[3-[[2-(1,4-Benzodioxan-5-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate,

1-[3-[[1,4-Benzodioxan-5-ylmethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate,

1-(4-Fluorophenyl)-1-[3-[4-(2-methoxyphenyl)piperazinyl]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[methyl[2-(2-methoxyphenoxy)ethyl]amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[methyl[2-(3-methoxyphenoxy)ethyl]amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

(*S*)-1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(1*H*-Indol-3-yl)butyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran,

(*S*)-1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indol-3-yl)propyl]methylamino]propyl]-1-phenyl-1,3-dihydroisobenzofuran,

5-[3-[[3-(1-Phenyl-1,3-dihydroisobenzofuran-1-yl)propyl]methylamino]propyl]-1,4-benzodioxane,

5-[3-[[3-[1-(3-Chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

5-[3-[[3-[1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

5-[3-[[3-[1-(3-Trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

1-[3-[[3-(1,4-Benzodioxan-5-yl)propyl]methylamino]propyl]-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[4-(1*H*-Indol-4-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[4-(1*H*-Indol-5-yl)piperazinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[4-(1*H*-Indol-3-yl)piperidinyl]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

5-[3-[[3-[-5-Fluoro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl]methylamino]propyl]-1,4-benzodioxane,

1-[3-[[2-(1*H*-Indolyl-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-(3-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-(2-methoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)- 1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(2,5-Dimethoxyphenyl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(1*H*-Indolyl-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[2-phenoxyethyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenyl)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(2-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl]methylamino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-(4-Fluorophenyl)-1-[3-[[3-(3-methoxyphenoxy)propyl](prop-2-en-1-yl)amino]propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[(2-Benzyloxyethyl)methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[(2-Benzyloxyethyl)(prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indolyl-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indolyl-3-yl)propyl](2-propynyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indolyl-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(7-Fluoro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

5-Fluoro-1-[3-[[3-(5-methyl -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran,

5-Fluoro-1-[3-[[3-(7-fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran,

1-[3-[[3-(5-Methyl -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(5-methyl -1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(7-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(5-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(7-fluoro-1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl] - 5-fluoro -1-(4-fluorophenyl) -1,3-dihydroisobenzofuran,

1-[3-[[4-(5-Methyl -1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(5-methyl -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(7-fluoro -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(5-fluoro -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(7-Chloro -1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Chloro-1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5,7-Difluoro -1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Fluoro -1*H*-indol-3-yl)butyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Chloro -1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5,7-Difluoro -1*H*-indol-3-yl)propyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Bromo -1*H*-indol-3-yl)ethyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Bromo -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Bromo -1*H*-indol-3-yl)ethyl]ethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Bromo -1*H*-indol-3-yl)butyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Bromo -1*H*-indol-3-yl)propyl]methylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[2-(5-iodo -1*H*-indol-3-yl)ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[Ethyl[3-(5-iodo -1*H*-indol-3-yl)propyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[2-[[4-(5-Chloro -1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[2-[[4-(5-Bromo -1*H*-indol-3-yl)butyl]methylamino]ethyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5,7-Difluoro -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(7-Chloro -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Chloro -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Bromo -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Methyl -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-Iodo -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-*t*-Butyl -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[4-[[2-(5-*i*-Propyl -1*H*-indol-3-yl)ethyl]methylamino]butyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Methyl -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Fluoro -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(7-Fluoro -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Fluoro -1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(7-Fluoro -1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Chloro -1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5,7-Difluoro -1*H*-indol-3-yl)ethyl]-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-[5-(2-Propyl)-1*H*-indol-3-yl]ethyl]-2-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(4-Fluoro-7-methyl-1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(4-Chloro-7-methyl-1*H*-indol-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ,

1-[3-[[3-(5-Chloro -1*H*-indol-3-yl)propyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)ethyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(7-Fluoro -1*H*-indol-3-yl)propyl](2-furylmethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(7-Carboxy-1*H*-indol-3-yl)butyl](prop-2-en-1-yl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-[5-Bromo-1*H*-indol-3-yl]ethyl]-propylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(1*H*-Indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Methyl-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5-Fluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)propyl]- 2-furylmethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Methyl-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[3-(5-Fluoro-1*H*-indol-3-yl)propyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[2-(5,7-Difluoro-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[[4-(5-Pyrrolo[3,2-*h*]-1*H*-quinolin-3-yl)butyl]- 2-furylmethylamino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile,

1-[3-[2-Phenoxyethyl[2-[5-(2-propyl)-1*H*-indol-3-yl]ethyl]amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile or

1-[3-[[2-(5-Bromo-1*H*-indol-3-yl)ethyl](2-phenoxyethyl)amino]propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile

or an acid addition salt thereof.

31. A pharmaceutical composition comprising a compound according to claims 1 to 30 or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

32. The use of a compound according to claims 1 to 30 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of a disorder or disease responsive to the effect of 5-HT_{1A} receptors.

33. The use of a compound according to claim 32 wherein the medicament is for the treatment of depression, psychosis, anxiety disorders, panic disorder, obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders and social phobia.

34. A method for the treatment of a disorder or disease of living animal body, including a human, which is responsive to the effect of 5-HT_{1A} receptors comprising administering to such a living animal body, including a human, a therapeutically effective amount of a compound according to claims 1 to 30 or a pharmaceutically acceptable acid addition salt thereof.

35. A method of treatment according to claim 34 where the disorder or disease is depression, psychosis, anxiety disorders, panic disorder, obsessive compulsive disorder, impulse control disorder, alcohol abuse, aggression, ischaemia, senile dementia, cardiovascular disorders or social phobia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00676

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87, A61K 31/343
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 2657013 A1 (KEFALAS A/S), 28 July 1977 (28.07.77) --	1-32
A	GB 1173312 A (KEFALAS A/S), 10 December 1969 (10.12.69) --	1-32
A	WO 9518118 A1 (THE UPJOHN COMPANY), 6 July 1995 (06.07.95) --	1-32

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2000	17 -04- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00676

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **34-35**
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant. this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant. this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2657013 A1	28/07/77	AT 359488 B	10/11/80
		AT 360001 B	10/12/80
		AT 360002 B	10/12/80
		AT 571979 A	15/05/80
		AT 572079 A	15/05/80
		AT 947276 A	15/04/80
		AU 509445 B	15/05/80
		AU 2107377 A	13/07/78
		BE 850401 A	14/07/77
		CA 1094087 A	20/01/81
		CH 626886 A	15/12/81
		CH 632258 A	30/09/82
		CH 632259 A	30/09/82
		DK 13177 A	15/07/77
		ES 454980 A	01/04/78
		FI 63754 B,C	29/04/83
		FI 770073 A	15/07/77
		FR 2338271 A,B	12/08/77
		GB 1526331 A	27/09/78
		IE 44055 B	29/07/81
		JP 1368581 C	11/03/87
		JP 52105162 A	03/09/77
		JP 61035986 B	15/08/86
		NL 192451 B,C	01/04/97
		NL 7700244 A	18/07/77
		NO 147243 B	22/11/82
		NO 770109 A	15/07/77
		NZ 183001 A	02/06/78
		SE 429551 B,C	12/09/83
		SE 7614201 A	15/07/77
		US 4136193 A	23/01/79
		ZA 7700057 A	30/11/77
GB 1173312 A	10/12/69	BE 695302 A	14/08/67
		CH 495975 A	15/09/70
		CH 511828 A	31/08/71
		DE 1593918 A	27/04/72
		DK 120640 B	28/06/71
		DK 120761 B	12/07/71
		DK 120762 B	12/07/71
		DK 120956 B	09/08/71
		DK 121026 B	23/08/71
		FR 1514754 A	00/00/00
		NL 6703332 A	18/09/67
		NO 121896 B	26/04/71
		SE 354862 B	26/03/73
		US 3523124 A	04/08/70
		US 3629444 A	21/12/71

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9518118 A1	06/07/95	AT 182590 T	15/08/99
		AU 684874 B	08/01/98
		AU 1257195 A	17/07/95
		CA 2176722 A	06/07/95
		CN 1139431 A	01/01/97
		DE 69419778 D	00/00/00
		EP 0737189 A,B	16/10/96
		SE 0737189 T3	
		ES 2133714 T	16/09/99
		IL 111940 D	00/00/00
		JP 9507224 T	22/07/97
		NZ 277373 A	28/07/98
		US 5877317 A	02/03/99
		ZA 9409927 A	13/06/96

J Clin Psychiatry. 1995 Nov;56(11):502-5.

Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence.

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BACKGROUND: Posttraumatic stress disorder (PTSD) often co-occurs with alcohol dependence, yet little is known about treatment of this comorbidity. The serotonin selective reuptake inhibitors have been shown preliminarily to be effective in decreasing symptoms of PTSD but have not been studied in individuals with comorbid alcohol dependence. This is of particular interest as the SSRIs also have a modest effect in decreasing alcohol consumption. METHOD: In this preliminary trial, nine subjects with comorbid PTSD and alcohol dependence were treated in an open-label trial with sertraline for a 12-week period. Symptoms of PTSD and depression were monitored monthly with the Impact of Event Scale and the Hamilton Rating Scale for Depression (HAM-D). Alcohol consumption was monitored by a self-report instrument (Time-Line Follow-Back). RESULTS: There were significant decreases in all three symptom clusters of PTSD measured by overall PTSD symptom scores ($p < \text{or} = .001$) and in HAM-D scores ($p < \text{or} = .001$) during the follow-up period. Days of abstinence increased and average number of drinks decreased during the follow-up period. Four subjects claimed total abstinence during the follow-up period. CONCLUSION: While limited by small sample size and the open-label, nonblinded study design, this study suggests that sertraline may be useful in the treatment of PTSD complicated by alcoholism. The medication was well tolerated and subjects showed improvement in PTSD symptoms as well as decreased alcohol consumption. A controlled trial of sertraline in this population would be of interest.

Publication Types:

- Clinical Trial

PMID: 7592501 [PubMed - indexed for MEDLINE]

Int Clin Psychopharmacol. 1996 Jun;11(2):109-17.

Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics.

Janiri L, Gobbi G, Mannelli P, Pozzi G, Serretti A, Tempesta E.

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Compulsivity in alcohol-dependent patients is a frequent cause of early relapse in the post-detoxification period. The present study is a 2-month trial on detoxified alcoholics undergoing a double-blind placebo-controlled treatment with fluoxetine (20 mg/day). The rating instruments were the Hamilton Depression and Anxiety Scales, a visual analogue scale for alcohol craving and an original scale for evaluating alcohol withdrawal. The abstinence rate for fluoxetine-treated patients was significantly higher than in the placebo group, whereas no difference between treatments was found on the rating scales. Medical problems, additional psychiatric diagnoses, and family alcoholism were negatively correlated with abstinence. Two subgroups of patients having significantly different characteristics were identified as to the outcome, by means of cluster analysis. They are likely to represent two different stages in the evolution of alcoholism. Our results show that, independently from craving, fluoxetine at antidepressant doses is able to prevent relapses in weaned alcoholics. The anticompulsive therapy can positively influence the short-term outcome, while other factors are negatively associated with abstinence.

Publication Types:

- Clinical Trial
- Controlled Clinical Trial

PMID: 8803648 [PubMed - indexed for MEDLINE]

International Clinical Psychopharmacology, 1992, **6 Suppl. 5**, 4

Introduction

The development in psychopharmacological treatment has placed serotonin as an important neurotransmitter in various psychiatric disorders. The 5-HT reuptake inhibitors seem to be effective in a range of different syndromes such as melancholia, major depression, atypical depression, dysphoria, recurrent brief depression, panic disorder, obsessive compulsive disorders, kleptomania, dementia, pain and alcoholism.

Due to this wide range of syndromes in which effect is reported, it has been suggested, that 5-HT uptake inhibitors should be named emotional stabilizers rather than antidepressants. It is a question whether serotonin plays a specific role in these syndromes, or the 5-HT uptake inhibitors influence a pathway common for all above mentioned syndromes. Maybe we are not even close to finding the central pathogenic mechanism for psychiatric disorders. By means of the selective substances available today, we have a method which leads us to a better understanding of the biology underlying the syndromes. The important issue is, however, that the selective drugs, i.e. 5-HT uptake inhibitors, are clinically effective and of benefit to the patients.

Citalopram is a 5-HT uptake inhibitor, the most selective marketed today. Citalopram has an excellent pharmacokinetic profile, a half-life of about 36 h and a minimal risk of interaction. Further to this, citalopram has only few, mild and transient side effects and is therefore well accepted generally, and also by groups who are sensitive to adverse effects. Citalopram is proven to be effective in depressive patients and excellent results are reported when treating elderly depressed patients with and without senile dementia. Patients suffering from panic disorder have also been treated with good results and high tolerability.

This publication contains proceedings from a symposium held in Florence, Italy, 11 June 1991 at the 5th World Congress of Biological Psychiatry and two further papers. A review of diagnoses in which 5-HT uptake inhibitors are reported effective is given. Serotonin in panic disorder is dealt with in detail. The difference in pharmacokinetic profile between 5-HT uptake inhibitors is reviewed with emphasis on citalopram. The clinical effect of citalopram in depression is illustrated by means of a meta-analysis, and the effect of citalopram in elderly patients is also presented. A view into the future treatment of depression was given as an introduction to the last part of the programme.

In addition, some recent placebo controlled short-term data for citalopram and preliminary evidence on the citalopram efficacy in relapse prevention is also described.

As chairman of the symposium, I express my sincere thanks to the speakers and authors for their contributions.

Rasmus Fog

International Clinical Psychopharmacology, 1992, **6 Suppl. 5**, 5–12

Potential Indications for the Selective Serotonin Reuptake Inhibitors

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The selective serotonin reuptake inhibitors (SSRIs) include fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline. These medications may be effective for a variety of indications. The literature clearly supports their efficacy in some of these conditions in major depression. Data concerning their use in other areas is clearly preliminary but promising. These include reports of treatment of obsessive–compulsive disorder, atypical depression, panic disorder, premenstrual tension, eating disorders, substance use disorders, chronic pain, dementia, and personality disorders with aggressive or impulsive features. The variety of clinical uses for the SSRIs may compel re-examination of traditional diagnostic categories and theories of how antidepressants work.

Introduction

The selective serotonin reuptake inhibitors (SSRIs) are an important new class of medications in clinical psychiatry. The class includes fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline. There is a large body of literature supporting their efficacy in major depression (Boyer and Feighner, 1991). As these compounds come into extensive use reports are emerging of their possible efficacy in a wider range of disorders. This review will briefly note some of these areas. The intent will not be to argue that the SSRIs are effective for all of these indications. The lack of controlled data clearly does not allow such a conclusion. Instead the aim will be to alert the reader to areas that bear watching and to consider the implications of these findings.

Obsessive–compulsive disorder (OCD)

A number of double-blind studies of sertraline and fluvoxamine in obsessive–compulsive disorder have been reported. With the exception of one small study (Jenike *et al.*, 1990*a*) these have shown clinically and statistically significant effects in OCD (Perse *et al.*, 1987; Bick *et al.*, 1989; Goodman, *et al.*, 1989; Chouinard *et al.*, 1990; Jenike *et al.*, 1990*b*). One study found fluvoxamine to be significantly superior to desipramine, a relatively more potent noradrenergic uptake inhibitor (Goodman *et al.*, 1990). Fluoxetine has also been studied in a number of open trials with encouraging results (Fontaine *et al.*, 1985; Turner *et al.*, 1985; Jenike *et al.*, 1989; Levine *et al.*, 1989*a*, *b*; Liebowitz *et al.*, 1990; Riddle *et al.*, 1990).

A number of disorders which share features with OCD may also respond to SSRIs. Fallon and colleagues treated seven patients with excessive religious scrupulosity for at

least 8 weeks with fluoxetine or clomipramine. At the end of the trial 5/7 were much improved. These results suggest that extreme moral or religious concerns may be a form of OCD and may be treatable with serotonin reuptake blockers (Fallon *et al.*, 1990). Benarroche reported an 80% response rate of trichotillomania to fluoxetine. All patients relapsed after medication was withdrawn (Parker, 1982). Viswanathan described a patient who experienced severe, recurrent, intrusive, but ego-syntonic fears that she or someone in her family had cancer. This was successfully relieved in two separate trials of fluoxetine, 20 mg b.i.d., but not by desipramine or buspirone (Viswanathan *et al.*, 1991).

Atypical depression

Atypical depression is an important, if imprecisely defined, clinical concept. Some evidence suggests that monoamine oxidase inhibitors (MAOIs) are superior to tricyclic antidepressants for these patients. However use of the MAOIs is limited by the need for dietary restrictions and concern for drug interactions. Pande *et al.* randomly assigned 27 patients with atypical depression as defined by Quitkin *et al.* to 6 weeks of double-blind treatment with fluoxetine 20–60 mg daily or phenelzine, 45–90 mg daily. The results showed 92% response with fluoxetine and 67% with phenelzine. Phenelzine patients also had significantly more side effects. More patients elected to stay on fluoxetine than phenelzine at the end of the trial (Pande *et al.*, 1991).

Panic disorder

Humble and colleagues treated 20 panic disorder patients with citalopram, up to 60 mg/day, in an 8 week open study. Citalopram appeared effective and well-tolerated (Humble *et al.*, 1989). Similar positive effects were reported in two open trials of fluoxetine (Gorman *et al.*, 1987; Schneier *et al.*, 1990). One controlled study has compared fluvoxamine with maprotiline, a noradrenaline uptake inhibitor, in panic disorder. Fluvoxamine was significantly effective but maprotiline was not (Den-Boer and Westenberg, 1988).

Premenstrual tension (PMS)

Two double-blind placebo-controlled studies have shown fluoxetine to significantly decrease the affective symptoms accompanying PMS (Rickels *et al.*, 1990; Stone *et al.*, 1990). However a study with fluvoxamine failed to show significant differences from placebo (Veeninga *et al.*, 1990). This may have been due to the strong placebo effect in this study or it may suggest that all SSRIs are not equally effective in this condition.

Personality disorders

Markovitz and associates treated 22 patients with borderline or schizotypal personality disorders in an open, 12-week trial of fluoxetine. All had initially sought help for anxiety or depression and 13 met criteria for major depression. There were significant reductions in self-injury and in scores on the Hopkins symptom checklist in patients with either or

both diagnoses (Markovitz, *et al.*, 1991). Two open studies of fluoxetine have also reported significant improvement in patients with severe borderline personality disorder (Cornelius *et al.*, 1990; Norden, 1991). There are however no controlled studies.

Substance abuse

Naranjo and colleagues tested citalopram in 39 non-depressed males who were early problem drinkers. Citalopram, 20 mg/day, did not show an effect but 40 mg/day decreased the number of drinks consumed and increased the number of abstinent days (Naranjo *et al.*, 1987). These same investigators found similar results with other serotonin reuptake blockers (Naranjo and Sellers, 1989).

Some evidence suggests that fluoxetine may antagonize the reinforcing properties of cocaine (Richardson and Roberts, 1991). Pollack and Rosenbaum gave fluoxetine to 11 cocaine-abusing heroin addicts in a methadone maintenance program. Of the eight patients who completed the trial, five were successfully treated for cocaine use. They concluded that fluoxetine may be a useful addition in the treatment of cocaine abuse (Pollack and Rosenbaum, 1991).

Eating disorders

Weight loss is a common side effect of the SSRIs. Several studies have suggested that fluoxetine or sertraline may be a useful adjunct in the treatment of obesity in non-depressed patients. Fortunately, the degree of weight loss appears to be proportional to the degree of initial obesity (Levine et al., 1987; Orzack *et al.*, 1990), so that weight loss in normal or underweight individuals is rarely a problem.

Clark and Rosenblatt studied 80 obese diabetic patients. Sertraline (150 mg/day) was associated with significantly more weight loss than placebo (2.9 vs. 0.76 kg) (Clark and Rosenblatt, 1989). Similarly, Feighner and Rosenblatt reported significantly more weight loss with sertraline, 50–200 mg/day, than placebo in 150 non-depressed obese outpatients (Feighner and Rosenblatt, 1989).

Weight loss with fluoxetine is associated with higher doses than usually used for depression, in the range of 40–60 mg/day (Levine, *et al.*, 1989*a*). Ferguson and Feighner found that fluoxetine (average 65 mg/day) produced significantly more weight loss than placebo among 150 non-depressed obese outpatients. Fluoxetine was also associated with a trend for more weight loss than benzphetamine (Ferguson and Feighner, 1987). Marcus and colleagues reported that patients treated with 60 mg/day of fluoxetine in addition to behavior therapy lost more weight than those treated with behavior therapy plus placebo (Marcus *et al.*, 1990).

Maintenance of weight loss is a problem with the SSRIs, as it is with other weight-loss strategies. Darga and co-workers compared diet plus either fluoxetine or placebo in the treatment of 45 non-depressed obese patients. The fluoxetine-treated patients lost significantly more weight, but had a tendency to regain it. At the end of 1 year there were no significant differences between the fluoxetine and placebo groups (Darga *et al.*, 1991).

The SSRIs may have beneficial effects in other eating disorders. Enas and colleagues compared two doses of fluoxetine in 382 outpatient bulimic women. At 60 mg/day fluoxetine was significantly superior to placebo. Fluoxetine 20 mg/day had an intermediate

effect (Enas *et al.*, 1989). This dose-response effect is similar to that noted above for weight loss with fluoxetine.

Weltzin and colleagues reported on 31 patients with chronic anorexia nervosa who were treated with fluoxetine for an average of 11 months. During the study 29 patients (94%) maintained their body weight at or above 85% average body weight for height. Global Response was judged to be good in 10, partial in 17 and poor in 6. Paradoxically, patients who were partial or poor responders were significantly more depressed at baseline than good responders (Weltzin *et al.*, 1991). This suggests that fluoxetine's effect may have been independent of its antidepressant activity. Gwirtsman and associates reported that six patients with chronic anorexia nervosa showed improved mood and weight gain with fluoxetine (Gwirtsman *et al.*, 1990). Ferguson reported successful use of fluoxetine in another patient with anorexia nervosa (Ferguson, 1987).

Other potential indications

Goldman and Janecek gave fluoxetine, 20 mg/day, to eight patients with schizophrenia in an open trial (Goldman and Janecek, 1990). Clinical state improved in all patients. Violent incidents decreased, while participation in programs and socialization increased. The addition of fluoxetine to neuroleptic medication has also been reported to be helpful in other patients with chronic schizophrenia (Goff *et al.*, 1990; Lindenmayer *et al.*, 1990).

Kafka reported that 9/10 men with DSM-III-R non-paraphilic sexual addiction or paraphilias had improved sexual behaviors while treated with fluoxetine, imipramine, or lithium (Kafka, 1991*a*). Kafka also reported that fluoxetine successfully treated a rapist with intrusive and persistent paraphilic rape fantasies. Symptoms of impulsiveness, anxiety and depression were also markedly improved (Kafka, 1991*b*). Another investigator reported the successful use of fluoxetine in treatment of a fetish (Lorefice, 1991).

Todd reported three cases of autism in which fluoxetine, 20 mg/day, was helpful in reducing behaviors such as stereotypies rituals, and violent outbursts (Todd, 1991). Ghaziuddin and colleagues presented four more cases of autism in which fluoxetine was helpful, especially in the presence of concomitant depression (Ghaziuddin *et al.*, 1991).

The SSRIs also improve some of the emotional and behavioral symptoms that accompany dementia (Nyth *et al.*, 1987, 1989; Martin *et al.*, 1989; Sobin *et al.*, 1989). Whether there is any primary improvement in memory function is unsettled.

Hanzel and associates compared fluoxetine with protriptyline in 12 patients with obstructive sleep apnea. Both drugs decreased periods of apnea and hypopneas, but fluoxetine was better tolerated (Hanzel *et al.*, 1991).

Pain is another area in which the SSRIs may be helpful. Theesen and March (1989) reported a patient with painful diabetic neuropathy and major depression, both of which responded to fluoxetine. Fluoxetine may also have some use in the treatment of headache (Diamond and Freitag, 1989) and fibrositis (Geller, 1989).

Discussion

An important theoretical question is how one class of medication could be helpful for such a disparate group of disorders. Part of this dilemma is artifactual: it is relatively common for patients with one disorder, for example borderline personality disorder, to present with features of other disorders. In this case the SSRI may be treating a feature of an associated disorder and contributing only indirectly to improvement in another.

Another hypothesis is one put forward by Van Praag and others; that abnormal serotonin function affects behavior in ways that cross traditional nosologic boundaries. For example, disturbed serotonin function may be related to depressed mood, anxiety, impulsivity, and aggression (Apter *et al.*, 1990). Many of the conditions for which the SSRIs are helpful have varying degrees of these features. The implication of this theory is that traditional nosologic boundaries may need to be re-examined in light of this biochemical and pharmacologic data.

A related possibility is that abnormalities in serotonin function may only begin a pathologic process, the ultimate form of which is shaped by the social environment, intrapsychic factors or other biological conditions. This is an interesting possibility as it is reminiscent of earlier psychodynamic formulations regarding symptom "choice".

Another hypothesis is that SSRIs may have a therapeutic effect which is unrelated to the etiology of the disorder. There are many examples of illnesses in which effective treatments do not act on the cause of the illness. Diuretics are helpful for hypertension although high blood pressure is rarely, if ever, caused by water or salt retention. Insulin is used in type II diabetes even though the pathology lies in sub-sensitivity to insulin rather than lack of insulin. Histamine-1 receptor blockers and antacids are mainstays of therapy for gastrointestinal ulcers although ulcers are not caused by an excess of histamine and only rarely by excessive acid production. These speculations on the apparently broad range of indications for the SSRIs are also of course not mutually exclusive. It will be very interesting to follow these areas to see which alternatives are supported.

References

Apter, A., Van-Praag, H.M., Plutchik, R., *et al.* (1990). Interrelationships among anxiety, aggression, impulsivity, and mood: a serotonergically linked cluster? *Psychiatry Research*, **32**, 191–199.

Bick, P.A. and Hackett, E. (1989). Sertraline is effective in obsessive–compulsive disorder. *In* "Psychiatry Today: VIII World Congress of Psychiatry Abstracts" (Eds C.N. Stefanis, C.R. Soldatos and A.D. Rabavilas), p. 152. Elsevier, New York.

Boyer, W.F. and Feighner, J.P. (1991). The efficacy of selective serotonin reuptake inhibitors in depression. *In* "Selective Serotonin Reuptake Inhibitors" (Eds J.P. Feighner and W.F. Boyer), pp. 89–108. Wiley, Chichester.

Chouinard, G., Goodman, W., Greist, J., *et al.* (1990). Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive–compulsive disorder. *Psychopharmacology Bulletin*, **26**, 279–284.

A multicenter study of sertraline in the treatment of diabetic obesity. Paper presented at Progress in the Treatment of Simple and Complicated Obesity, Lisbon, 19 September, 1989.

Cornelius, J.R., Soloff, P.H., Perel, J.M., *et al.* (1990). Fluoxetine trial in borderline personality disorder. *Psychopharmacology Bulletin*, **26**, 151–154.

Darga, L.L., Carroll-Michals, L., Botsford, S.J., *et al.* (1991). Fluoxetine's effect on weight loss in obese subjects. *American Journal of Clinical Nutrition*, **54**, 321–325.

Den-Boer, J.A. and Westenberg, H.G. (1988). Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder; a double-blind comparative study with fluvoxamine and maprotiline. *International Clinical Psychopharmacology*, **3**, 59–74.

Diamond, S. and Freitag, F.G. (1989). The use of fluoxetine in the treatment of headache. *Clinical Journal of Pain*, **5**, 200–201.

Fluoxetine in bulimia nervosa: double-blind study. New Research Program and Abstracts, American Psychiatric Association 142nd Annual Meeting, p. 204.

Fallon, B.A., Liebowitz, M.R., Hollander, E., *et al.* (1990). The pharmacotherapy of moral or religious scrupulosity. *Journal of Clinical Psychiatry*, **51**, 517–521.

A double-blind placebo-controlled study of sertraline in the treatment of obesity. Paper presented at Progress in the Treatment of Simple and Complicated Obesity, Lisbon, 19 September 1989.

Ferguson, J.M. (1987). Treatment of an anorexia nervosa patient with fluoxetine. *American Journal of Psychiatry*, **144**, 1239.

Ferguson, J.M. and Feighner, J.P. (1987). Fluoxetine-induced weight loss in overweight non-depressed humans. *International Journal of Obesity*, **11** (Suppl. 3), 163–170.

Fontaine, R. and Chouinard, G. (1985). Fluoxetine in the treatment of obsessive–compulsive disorder. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **9**, 5–6, 605–608.

Geller, S.A. (1989). Treatment of fibrositis with fluoxetine hydrochloride (Prozac). *American Journal of Medicine*, **87**, 594–595.

Ghaziuddin, M., Tsai, L. and Ghaziuddin, N. (1991). Fluoxetine in autism with depression (letter). *Journal of the American Academy of Child Adolescent Psychiatry*, **30**, 508–509.

Goff, D.C., Brotman, A.W., Waites, M., *et al.* (1990). Trial of fluoxetine added to neuroleptics for treatment-resistant schizophrenic patients. *American Journal of Psychiatry*, **147**, 492–494.

Goldman, M.B. and Janecek, H.M. (1990). Adjunctive fluoxetine improves global function in chronic schizophrenia. *Journal of Neuropsychiatry and Clinical Neuroscience*, **2**, 429–431.

Goodman, W.K., Price, L.H., Rasmussen, S.A., *et al.* (1989). Efficacy of fluvoxamine in obsessive–compulsive disorder. A double-blind comparison with placebo. *Archives of General Psychiatry*, **46**, 36–44.

Goodman, W.K., Price, L.H., Delgado, P.L., *et al.* (1990). Specificity of serotonin reuptake inhibitors in the treatment of obsessive–compulsive disorder: comparison of fluvoxamine and desipramine. *American Journal of Psychiatry*, **47**, 577–585.

Gorman, J.M., Liebowitz, M.R., Fyer, A.J., *et al.* (1987). An open trial of fluoxetine in the treatment of panic attacks (published erratum appears in *Journal of Clinical Psychopharmacology*, 1988, **8**, 13). *Journal of Clinical Psychopharmacology*, **7**, 329–332.

Gwirtsman, H.E., Guze, B.H., Yager, J., *et al.* (1990). Fluoxetine treatment of anorexia nervosa: an open clinical trial. *Journal of Clinical Psychiatry*, **51**, 378–382.

Hanzel, D.A., Proia, N.G. and Hudgel, D.W. (1991). Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest*, **100**, 416–421.

Humble, M., Koczkas, C. and Wistedt, B. (1989). Serotonin and anxiety: an open study of citalopram in panic disorder. *In* "Psychiatry Today: VIII World Congress of Psychiatry Abstracts" (Eds C.N. Stefanis, C.R. Soldatos and A.D. Rabavilas), p. 151. Elsevier, New York.

Jenike, M.A., Buttolph, L., Baer, L., *et al.* (1989). Open trial of fluoxetine in obsessive–compulsive disorder. *American Journal of Psychiatry*, **146**, 909–911.

Jenike, M.A., Baer, L., Summergrad, P., *et al.* (1990*a*). Sertraline in obsessive–compulsive disorder: a double-blind comparison with placebo. *American Journal of Psychiatry*, **147**, 923–928.

Jenike, M.A., Hyman, S., Baer, L., *et al.* (1990*b*). A controlled trial of fluvoxamine in obsessive–compulsive disorder: implications for a serotonergic theory. *American Journal of Psychiatry*, **147**, 1209–1215.

Kafka, M.P. (1991*a*). Successful antidepressant treatment of nonparaphilic sexual addictions and paraphilias in men. *Journal of Clinical Psychiatry*, **52**, 60–65.

Kafka, M.P. (1991*b*). Successful treatment of paraphilic coercive disorder (a rapist) with fluoxetine hydrochloride. *British Journal of Psychiatry*, **158**, 844–847.

Levine, L.R., Rosenblatt, S. and Bosomworth, J. (1987). Use of a serotonin re-uptake inhibitor, fluoxetine, in the treatment of obesity. *International Journal of Obesity*, **11** (Suppl. 3), 185–190.

Levine, L.R., Enas, C.G., Thompson, W.L., *et al.* (1989*a*). Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: a dose-response study. *International Journal of Obesity*, **13**, 635–645.

Levine, R., Hoffman, J.S., Knepple, E.D., *et al.* (1989*b*). Long-term fluoxetine treatment of a large number of obsessive–compulsive patients. *Journal of Clinical Psychopharmacology*, **9**, 281–283.

Liebowitz, M.R., Hollander, E., Fairbanks, J., *et al.* (1990). Fluoxetine for adolescents with obsessive–compulsive disorder. *Americal Journal of Psychiatry*, **147**, 370–371.

Lindenmayer, J.P., Vakharia, M. and Kanofsky, D. (1990). Fluoxetine in chronic schizophrenia. *Journal of Clinical Psychopharmacology*, **10**, 76.

Lorefice, L.S. (1991). Fluoxetine treatment of a fetish (letter). *Journal of Clinical Psychiatry*, **52**, 41.

Marcus, M.D., Wing, R.R., Ewing, L., *et al.* (1990). A double-blind, placebo-controlled trial of fluoxetine plus behaviour modification in the treatment of obese binge-eaters and non-binge-eaters. *American Journal of Psychiatry*, **147**, 876–881.

Markovitz, P.J., Calabrese, J.R., Schulz, S.C., *et al.* (1991). Fluoxetine in the treatment of borderline and schizotypal personality disorders. *American Journal of Psychiatry*, **148**, 1064–1067.

Martin, P.R., Adinoff, B., Eckardt, M.J., *et al.* (1989). Effective pharmacotherapy of alcoholic amnestic disorder with fluvoxamine. *Archives of General Psychiatry*, **46**, 617–624.

Naranjo, C.A., Sellers, E.M., Sullivan, J.T., *et al.* (1987). The serotonin uptake inhibitors attenuate ethanol intake. *Clinical Pharmacology and Therapeutics*, **41**, 266–274.

Naranjo, C.A. and Sellers, E.M. (1989). Serotonin uptake inhibitors attenuate ethanol intake in problem drinkers. *Recent Developments in Alcohol*, **7**, 255–266.

Norden, M.J. (1991). Borderline patients on maintenance fluoxetine. New Research Program and Abstracts, American Psychiatric Association 144th Annual Meeting, p. 122.

Nyth, A.L., Balldin, J., Elgen, K., *et al.* (1987). Treatment with Citalopram in dementia. Normalization of dexamethasone suppression test. *Nordisk Psykiatr Tidsskrift*, **41**, 423–429.

Nyth, A.L., Gottfries, C.G., Elgen, K., *et al.* (1989). The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. *In* "Psychiatry Today: VIII World Congress of Psychiatry Abstracts" (Eds C.N. Stefanis, C.R. Soldatos and A.D. Rabavilas), p. 503. Elsevier, New York.

Orzack, M.H., Friedman, L.M. and Marby, D.W. (1990). Weight changes on fluoxetine as a function of baseline weight in depressed outpatients. *Psychopharmacology Bulletin*, **26**, 327–330.

Pande, A.C., Haskett, R.F. and Greden, J.F. (1991). Double-blind comparison of fluoxetine and phenelzine in atypical depression. *Biological Psychiatry Supplement*, 29(9A), 117A–118A.

Parker, G. (1982). Re-searching and schizophrenogenic mother. *Journal of Nervous and Mental Diseases*, **170**, 452–462.

Perse, T.L., Greist, J.H., Jefferson, J.W., *et al.* (1987). Fluvoxamine treatment of obsessive–compulsive disorder. *American Journal of Psychiatry*, **144**, 1543–1548.

Pollack, M.H. and Rosenbaum, J.F. (1991). Fluoxetine treatment of cocaine abuse in heroin addicts. *Journal of Clinical Psychiatry*, **52**, 31–33.

Richardson, N.R. and Roberts, D.C. (1991). Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. *Life Sciences*, **49**, 833–840.

Rickels, K., Freeman, E.W., Sondheimer, S., *et al.* (1990). Fluoxetine in the treatment of premenstrual syndrome. *Current Therapeutic Research and Clinical Experiments*, **48**, 161–166.

Riddle, M.A., Hardin, M.T., King, R., *et al.* (1990). Fluoxetine treatment of children and adolescents with Tourette's and obsessive–compulsive disorders: preliminary clinical experience. *Journal of the American Academy of Child Adolescent Psychiatry*, **29**, 45–48.

Schneier, F.R., Liebowitz, M.R., Davies, S.O., *et al.* (1990). Fluoxetine in panic disorder. *Journal of Clinical Psychopharmacology*, **10**, 119–121.

Sobin, P., Schneider, L. and McDermot, H. (1989). Fluoxetine in the treatment of agitated dementia. *American Journal of Psychiatry*, **146**, 1636.

Stone, A.B., Pearlstein, T.B. and Brown, W.A. (1990). Fluoxetine in the treatment of premenstrual syndrome. *Psychopharmacology Bulletin*, **26**, 331–335.

Theesen, K.A. and Marsh, W.R. (1989). Relief of diabetic neuropathy with fluoxetine. DICP, **23**, 572–574

Todd, R.D. (1991). Fluoxetine in autism (letter). *American Journal of Psychiatry*, **148**, 1089.

Turner, S.M., Jacob, R.G., Beidel, D.C., *et al.* (1985). Fluoxetine treatment of obsessive–compulsive disorder. *Journal of Clinical Psychopharmacology*, **5**, 207–212

Veeninga, A.T., Westenberg, H.G. and Wesuten, J.T. (1990). Fluvoxamine in the treatment of menstrually related mood disorders. *Psychopharmacology (Berlin)*, **102**, 414–416.

Viswanathan, R. and Paradis, C. (1991). Treatment of cancer phobia with fluoxetine (letter). *American Journal of Psychiatry*, **148**, 1090.

Weltzin, T.E., Hsu, L.K.G. and Kaye, W.H. (1991). Continued open trial of fluoxetine in anorexia. New Research Program and Abstracts, American Psychiatric Association 144th Annual Meeting, pp. 123–124.

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Clinical Pharmacokinetics of Citalopram and Other Selective Serotonergic Reuptake Inhibitors (SSRI)

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The pharmacokinetics and clinical properties of clomipramine, the classic 5-HT uptake inhibiting antidepressant is well known. Within the last years, several new and more selective serotonin uptake inhibitors have been introduced in clinical practice, including trazodone, citalopram, paroxetine, femoxetine, fluvoxamine and fluoxetine. They differ by their chemical structure, and therefore, important differences can be expected with respect to their metabolism and kinetics in man. In this presentation, the following points will be addressed: Present knowledge about their metabolism and their kinetics, taking into account that most of them are racemates, whose clinical role is only partially understood, including that of the metabolites. It will further be examined whether they are candidates for a genetic polymorphism of metabolism of the debrisoquine-spartein-dextromethorphan type. This may e.g. be suspected for fluoxetine which interferes strongly with the metabolism of tricyclic antidepressants. Finally, data of the literature will be analysed about a possible relationship between the clinical efficacy of these drugs and their plasma levels, including those of their active metabolites.

Introduction

The classical tricyclic antidepressants have many similarities in pharmacodynamics and pharmacokinetics, as a consequence of their common chemical structure. Nevertheless, they differ widely in potency and selectivity and inhibition of the reuptake of serotonin and norepinephrine (Table 1). Within the last few years, several more potent and more selective serotonin reuptake inhibitors (SSRI) have been introduced as antidepressants in clinical practice or are still under investigation (Feighner and Boyer, 1991). These include citalopram, femoxetine, fluoxetine, fluvoxamine, paroxetine and sertraline, not to forget the earlier introduced drug trazodone for its selectivity but low potency (Table 1).

The pharmacological profile—chemical structure relationship of SSRIs

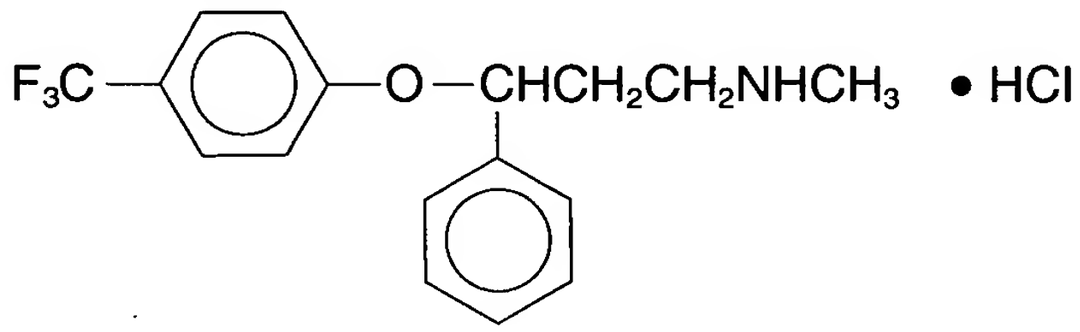
Among the tricyclic antidepressant drugs, clomipramine is considered to be the most potent 5-HT reuptake inhibitor *in vitro*. However, due to the presence of its metabolite demethylclomipramine, a potent norepinephrine reuptake inhibitor, the plasma concentrations of which often exceed those of the parent compound, clomipramine loses *in vivo* much of its selectivity. Among the new SSRIs, paroxetine is the most potent, and citalopram the most selective serotonin reuptake inhibitor. Citalopram's main metabolite,

PV 3453 DPP

PROZAC®
FLUOXETINE HYDROCHLORIDE

DESCRIPTION

Prozac® (fluoxetine hydrochloride) is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem™, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \bullet HCl$. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C Blue No. 1, and the 40-mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

Each tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, crospovidone, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the 10-mg tablet contains FD&C Blue No. 1 aluminum lake, and polysorbate 80.

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

Prozac Weekly™ capsules, a delayed release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant, antiobsessive-compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion

Systemic bioavailability — In man, following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The Pulvule, tablet, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food. Prozac Weekly capsules, a delayed release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate release formulations.

Protein binding — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* PRECAUTIONS).

Enantiomers — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism — Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical issues related to metabolism/elimination — The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including TCAs and other SSRIs, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* Drug Interactions *under* PRECAUTIONS).

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of

fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of Prozac.

Weekly dosing — Administration of Prozac Weekly once-weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of fluoxetine are in the range of the average concentration for 20 mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared with the once-daily regimen.

C_{max} for fluoxetine following the 90-mg dose was approximately 1.7-fold higher than the C_{max} value for the established 20 mg once-daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90-mg once-weekly dose and the last 20-mg once-daily dose were separated by 1 week, C_{max} values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90-mg weekly dose and the last 20-mg once-daily dose by 1 week (*see* DOSAGE AND ADMINISTRATION).

Liver disease — As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Renal disease — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (*see* Use in patients with concomitant illness *under* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Age

Geriatric pharmacokinetics — The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not

adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Pediatric pharmacokinetics (children and adolescents) — Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with major depressive disorder or obsessive compulsive disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with major depressive disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

CLINICAL TRIALS

Major Depressive Disorder

Daily Dosing

Adult — The efficacy of Prozac for the treatment of patients with major depressive disorder (≥18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Prozac was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies (N=671, randomized) comparing Prozac 20 mg and placebo have shown Prozac 20 mg daily to be effective in the treatment of elderly patients (≥60 years of age) with major depressive disorder. In these studies, Prozac produced a significantly higher rate of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤8. Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤7 during each of the last 3 weeks of open-label treatment and absence of major depressive disorder by DSM-III-R criteria) by the end of an initial 12-week open-treatment phase on Prozac 20 mg/day. These patients (N=298) were randomized to continuation on double-blind Prozac 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of major depressive disorder for 2 weeks or a modified HAMD-17 score of ≥14 for 3 weeks) was observed for patients taking Prozac compared with those on placebo.

Pediatric (children and adolescents) — The efficacy of Prozac 20 mg/day for the treatment of major depressive disorder in pediatric outpatients (N=315 randomized; 170 children ages 8 to <13, 145 adolescents ages 13 to ≤18) has been studied in two 8- to 9-week placebo-controlled clinical trials.

In both studies independently, Prozac produced a statistically significantly greater mean change on the Childhood Depression Rating Scale-Revised (CDRS-R) total score from baseline to endpoint than did placebo.

Subgroup analyses on the CDRS-R total score did not suggest any differential responsiveness on the basis of age or gender.

Weekly dosing for maintenance/continuation treatment

A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded (defined as having a modified HAMD-17 score of ≤9, a CGI-Severity rating of ≤2, and no longer meeting criteria for major depressive disorder) for 3 consecutive weeks at the end of 13 weeks of open-label treatment with Prozac 20 mg once daily. These patients were randomized to double-blind, once-weekly continuation treatment with Prozac Weekly, Prozac 20 mg once daily, or placebo. Prozac Weekly once weekly and Prozac 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of depressive symptoms) compared with placebo for a period of 25 weeks. However, the equivalence of these 2 treatments during continuation therapy has not been established.

Obsessive Compulsive Disorder

Adult — The effectiveness of Prozac for the treatment for obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once-a-day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. While there was no indication of a dose-response relationship for effectiveness in Study 1, a dose-response relationship was observed in Study 2, with numerically better responses in the 2 higher dose groups. The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined:

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies				
		Prozac		
Outcome Classification	Placebo	20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No change	64%	41%	33%	29%
Minimally improved	17%	23%	28%	24%
Much improved	8%	28%	27%	28%
Very much improved	3%	8%	12%	19%

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

Pediatric (children and adolescents) — In one 13-week clinical trial in pediatric patients (N=103 randomized; 75 children ages 7 to <13, 28 adolescents ages 13 to <18) with OCD, patients received Prozac 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks. The dose was then adjusted in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. Prozac produced a statistically significantly greater mean change from baseline to

endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

Bulimia Nervosa

The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 or 60 mg/day of Prozac or placebo in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day (once a day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these 3 studies, Prozac 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg vs placebo was present as early as Week 1 and persisted throughout each study. The Prozac-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between Prozac 60 mg and placebo on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment, for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

In a longer-term trial, 150 patients meeting (DSM-IV) criteria for bulimia nervosa, purging subtype, who had responded during a single-blind, 8-week acute treatment phase with Prozac 60 mg/day, were randomized to continuation of Prozac 60 mg/day or placebo, for up to 52 weeks of observation for relapse. Response during the single-blind phase was defined by having achieved at least a 50% decrease in vomiting frequency compared with baseline. Relapse during the double-blind phase was defined as a persistent return to baseline vomiting frequency or physician judgement that the patient had relapsed. Patients receiving continued Prozac 60 mg/day experienced a significantly longer time to relapse over the subsequent 52 weeks compared with those receiving placebo.

Panic Disorder

The effectiveness of Prozac in the treatment of panic disorder was demonstrated in 2 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia.

Study 1 (N=180 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 42% vs 28%, respectively.

Study 2 (N=214 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in a range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% vs 44%, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder

Prozac is indicated for the treatment of major depressive disorder.

Adult — The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (*see* CLINICAL TRIALS).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The effects of Prozac in hospitalized depressed patients have not been adequately studied.

The efficacy of Prozac 20 mg once daily in maintaining a response in major depressive disorder for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial.

The efficacy of Prozac Weekly once weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis provides the same level of protection from relapse as that provided by Prozac 20 mg daily (*see* CLINICAL TRIALS).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (*see* CLINICAL TRIALS).

The usefulness of the drug in adult and pediatric patients receiving fluoxetine for extended periods should be reevaluated periodically.

Obsessive-Compulsive Disorder

Adult — Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13-week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of OCD (*see* CLINICAL TRIALS).

OCD is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in a 13-week, dose titration, clinical trial in patients with OCD, as defined in DSM-IV (*see* CLINICAL TRIALS).

Bulimia Nervosa

Prozac is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa.

The efficacy of Prozac was established in 8- to 16-week trials for adult outpatients with moderate to severe bulimia nervosa, i.e., at least 3 bulimic episodes per week for 6 months (*see* CLINICAL TRIALS).

The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who responded during an 8-week acute treatment phase while taking Prozac 60 mg/day and were then observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled trial (*see* CLINICAL TRIALS). Nevertheless, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Panic Disorder

Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Prozac was established in two 12-week clinical trials in patients whose diagnoses corresponded to the DSM-IV category of panic disorder (*see* CLINICAL TRIALS).

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 or more of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) fear of losing control; 10) fear of dying; 11) paresthesias (numbness or tingling sensations); 12) chills or hot flashes.

The effectiveness of Prozac in long-term use, i.e., for more than 12 weeks, has not been established in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Prozac is contraindicated in patients known to be hypersensitive to it.

Monoamine oxidase inhibitors — There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY)] should be allowed after stopping Prozac before starting an MAOI.

Thioridazine — Thioridazine should not be administered with Prozac or within a minimum of 5 weeks after Prozac has been discontinued (*see* WARNINGS).

WARNINGS

Rash and possibly allergic events — In US fluoxetine clinical trials as of May 8, 1995, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis and including lupus-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Potential interaction with thioridazine — In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (*see* CONTRAINDICATIONS).

PRECAUTIONS

General

Anxiety and insomnia — In US placebo-controlled clinical trials for major depressive disorder, 12% to 16% of patients treated with Prozac and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with Prozac 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported, respectively, in 15% and 11% of patients treated with Prozac 60 mg and in 9% and 5% of patients treated with placebo.

Among the most common adverse events associated with discontinuation (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in major depressive disorder) (*see* Table 3).

Altered appetite and weight — Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with Prozac.

In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with Prozac because of anorexia or weight loss (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with Prozac because of anorexia (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with Prozac 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

Activation of mania/hypomania — In US placebo-controlled clinical trials for major depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of major depressive disorder (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with Prozac and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.7% of 10,782 patients reported mania/hypomania (*see also* Pediatric Use *under* PRECAUTIONS).

Seizures — In US placebo-controlled clinical trials for major depressive disorder, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD or bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of major depressive disorder. Prozac should be introduced with care in patients with a history of seizures.

Suicide — The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Because of well-established comorbidity between both OCD and major depressive disorder and bulimia and major depressive disorder, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with OCD or bulimia.

The long elimination half-lives of fluoxetine and its metabolites — Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Use in patients with concomitant illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma (*see* Renal disease *under* CLINICAL PHARMACOLOGY). Use of a lower or less frequent dose for renally impaired patients is not routinely necessary (*see* DOSAGE AND ADMINISTRATION).

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference with cognitive and motor performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Drugs metabolized by CYP2D6 — Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme 2D6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most drugs effective in the treatment of major depressive disorder, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 active enantiomers is comparable between poor and extensive metabolizers (*see* Variability in metabolism *under* CLINICAL PHARMACOLOGY).

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see* CONTRAINDICATIONS *and* WARNINGS).

Drugs metabolized by CYP3A4 — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

CNS active drugs — The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of Prozac and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Anticonvulsants — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between serotonin specific reuptake inhibitors (SSRIs) and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia. For thioridazine, see CONTRAINDICATIONS and WARNINGS.

Benzodiazepines — The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

Other drugs effective in the treatment of major depressive disorder — In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY, *and* Drugs metabolized by CYP2D6 *under* Drug Interactions).

Sumatriptan — There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised.

Potential effects of coadministration of drugs tightly bound to plasma proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Warfarin — Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Electroconvulsive therapy (ECT) — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

Carcinogenicity — The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively [approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis], produced no evidence of carcinogenicity.

Mutagenicity — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of fertility — Two fertility studies conducted in rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility.

Pregnancy — Pregnancy Category C

In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the MRHD of 80 mg on a mg/m^2 basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis). Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of Prozac on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

Pediatric Use

The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤18. (*see* CLINICAL TRIALS).

The efficacy of Prozac for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18 (*see* CLINICAL TRIALS).

The safety and effectiveness in pediatric patients <8 years of age in major depressive disorder and <7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤18) with major depressive disorder or OCD (*see* Pharmacokinetics *under* CLINICAL PHARMACOLOGY).

The acute adverse event profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse event profile observed in the 19-week major depressive disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine (*see* ADVERSE REACTIONS).

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height (p=0.004)

and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine.

Geriatric Use

US fluoxetine clinical trials as of May 8, 1995 (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been established (*see* CLINICAL TRIALS). For pharmacokinetic information in geriatric patients, see Age under CLINICAL PHARMACOLOGY. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (*see* Hyponatremia *under* PRECAUTIONS).

Hyponatremia

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Platelet Function

There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

ADVERSE REACTIONS

Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient

characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 1 enumerates the most common treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for Prozac and at least twice that for placebo within at least 1 of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US plus non-US controlled trials. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who participated in US major depressive disorder, OCD, and bulimia controlled clinical trials and US plus non-US panic disorder controlled clinical trials. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

Table 1: Most Common Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
Body System/ Adverse Event	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
Nervous System								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2
Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
Respiratory System								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2

Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence[2]	2	--	--	--	7	--	1	--
Abnormal ejaculation[2]	--	--	7	--	7	--	2	1

[1]Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

[2]Denominator used was for males only (N=690 Prozac major depressive disorder; N=410 placebo major depressive disorder; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia; N=162 Prozac panic; N=121 placebo panic).

--Incidence less than 1%.

Table 2: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
	Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
Body System/ Adverse Event[2]	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1

Thinking abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

[1]Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

[2]Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo ≥ Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined): abdominal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.

--Incidence less than 1%.

Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 3 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Table 3: Most Common Adverse Events Associated with Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)	Major Depressive Disorder (N=392)	OCD (N=266)	Bulimia (N=450)	Panic Disorder (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

[1]Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Other adverse events in pediatric patients (children and adolescents) — Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events (excluding those which appear in the body or footnotes of Tables 1 and 2 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

The most common adverse event (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for

fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary event associated with discontinuation was collected.

Events observed in Prozac Weekly clinical trials — Treatment-emergent adverse events in clinical trials with Prozac Weekly were similar to the adverse events reported by patients in clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% vs 3%, respectively) or taking Prozac 20 mg daily (10% vs 5%, respectively).

Male and female sexual dysfunction with SSRIs — Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Events Observed in Clinical Trials

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed in the body or footnotes of Tables 1 or 2 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient treated with Prozac and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole — *Frequent:* chest pain, chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome[1], photosensitivity reaction.

Cardiovascular System — *Frequent:* hemorrhage, hypertension, palpitation; *Infrequent:* angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare:* atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System — *Frequent:* increased appetite, nausea and vomiting; *Infrequent:* aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare:*

biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional — *Frequent:* weight gain; *Infrequent:* dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare:* alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare:* arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System — *Frequent:* agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder[2], psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System — *Infrequent:* asthma, epistaxis, hiccup, hyperventilation; *Rare:* apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses — *Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System — *Frequent:* urinary frequency; *Infrequent:* abortion[3], albuminuria, amenorrhea[3], anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation[3], fibrocystic breast[3], hematuria, leukorrhea[3], menorrhagia[3], metrorrhagia[3], nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage[3]; *Rare:* breast engorgement, glycosuria, hypomenorrhea[3], kidney pain, oliguria, priapism[3], uterine hemorrhage[3], uterine fibroids enlarged[3].

[1]Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
[2]Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
[3]Adjusted for gender.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema

nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled substance class — Prozac is not a controlled substance.

Physical and psychological dependence — Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Animal Experience

Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see* Management of Overdose).

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS).

Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (*PDR*).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Initial Treatment

Adult — In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

Pediatric (children and adolescents) — In the short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10 to 20 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

All patients — As with other drugs effective in the treatment of major depressive disorder, the full effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing

Systematic evaluation of Prozac in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see* CLINICAL TRIALS).

Weekly Dosing

Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established (*see* CLINICAL TRIALS).

Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the last daily dose of Prozac 20 mg (*see* Weekly dosing *under* CLINICAL PHARMACOLOGY).

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen *(see* CLINICAL TRIALS).

Switching Patients to a Tricyclic Antidepressant (TCA)

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Other drugs effective in the treatment of major depressive disorder *under* Drug Interactions).

Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping Prozac before starting an MAOI (*see* CONTRAINDICATIONS *and* PRECAUTIONS).

Obsessive-Compulsive Disorder

Initial Treatment

Adult — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine

or placebo (*see* CLINICAL TRIALS). In 1 of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

Pediatric (children and adolescents) — In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS).

In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended.

In lower weight children, treatment should be initiated with dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

All patients — As with the use of Prozac in the treatment of major depressive disorder, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

Bulimia Nervosa

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo (*see* CLINICAL TRIALS). Only the 60-mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments

for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment (*see* CLINICAL TRIALS). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Panic Disorder

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

The following products are manufactured by Eli Lilly and Company for Dista Products Company.

Prozac® Pulvules®, USP, are available in:

The 10-mg[1] Pulvule is opaque green and green, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body:

NDC 0777-3104-02 (PU3104[2]) – Bottles of 100
NDC 0777-3104-07 (PU3104[2]) – Bottles of 2000
NDC 0777-3104-82 (PU3104[2]) – 20 FlexPak™[3] blister cards of 31

The 20-mg[1] Pulvule is an opaque green cap and off-white body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body:

NDC 0777-3105-30 (PU3105[2]) – Bottles of 30
NDC 0777-3105-02 (PU3105[2]) – Bottles of 100
NDC 0777-3105-07 (PU3105[2]) – Bottles of 2000
NDC 0777-3105-33 (PU3105[2]) – (ID[4]100) Blisters
NDC 0777-3105-82 (PU3105[2]) – 20 FlexPak™[3] blister cards of 31

The 40-mg[1] Pulvule is an opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body:

NDC 0777-3107-30 (PU3107[2]) – Bottles of 30

Liquid, Oral Solution is available in:

20 mg[1] per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120[5]) – Bottles of 120 mL

The following products are manufactured and distributed by Eli Lilly and Company.

Prozac® Tablets are available in:

The 10-mg[1] tablet is green, elliptical shaped, and scored, with PROZAC 10 debossed on opposite side of score.

NDC 0002-4006-30 (TA4006) – Bottles of 30
NDC 0002-4006-02 (TA4006) – Bottles of 100

Prozac® Weekly™ Capsules are available in:

The 90-mg[1] capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

NDC 0002-3004-75 (PU3004) – Blister package of 4

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[1]Fluoxetine base equivalent.
[2]Protect from light.
[3]FlexPak™ (flexible blister card, Lilly).
[4]Identi-Dose® (unit dose medication, Lilly).
[5]Dispense in a tight, light resistant container.

Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

ANIMAL TOXICOLOGY

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

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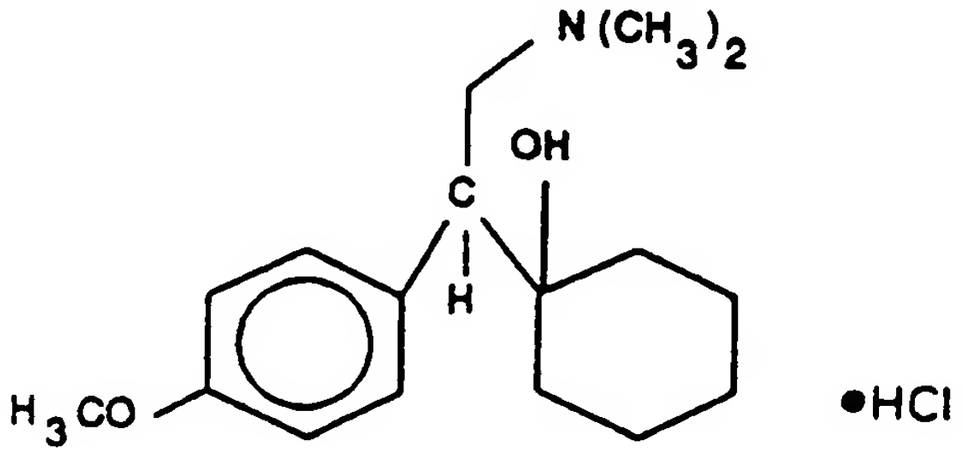
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Effexor (venlafaxine hydrochloride) is a structurally novel antidepressant for oral administration. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethyl-amino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ HCl. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.

Compressed tablets contain venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg, or 100 mg venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α-1 adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Food has no significant effect on the absorption of venlafaxine or on the formation of ODV.

The degree of binding of venlafaxine to human plasma is 27% ± 2% at concentrations ranging from 2.5 to 2215 ng/mL. The degree of ODV binding to human plasma is 30% ± 12% at concentrations ranging from 100 to 500 ng/mL. Protein-binding-induced drug interactions with venlafaxine are not expected.

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg total dose per day (administered on a q8h schedule). Plasma clearance, elimination half-life and steady-state volume of distribution were unaltered for both venlafaxine and ODV after multiple-dosing. Mean ± SD steady-state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and steady-state volume of distribution is 7.5 ± 3.7 L/kg and 5.7 ± 1.8 L/kg, respectively. When equal daily doses of venlafaxine were administered as either b.i.d. or t.i.d. regimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Age and Gender

A pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered due to age or gender differences. Dosage adjustment based upon the age or gender of a patient is generally not necessary (see **DOSAGE AND ADMINISTRATION**).

Liver Disease

In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects.

Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

Renal Disease
In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR = 10-70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR = 10-70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56%, compared to normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in these patients (see **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

The efficacy of Effexor (venlafaxine hydrochloride) as a treatment for major depressive disorder was established in 5 placebo-controlled, short-term trials. Four of these were 6-week trials in adult outpatients meeting DSM-III or DSM-III-R criteria for major depression: two involving dose titration with Effexor in a range of 75 to 225 mg/day (t.i.d. schedule), the third involving fixed Effexor doses of 75, 225, and 375 mg/day (t.i.d. schedule), and the fourth involving doses of 25, 75, and 200 mg/day (b.i.d. schedule). The fifth was a 4-week study of adult inpatients meeting DSM-III-R criteria for major depression with melancholia whose Effexor doses were titrated in a range of 150 to 375 mg/day (t.i.d. schedule). In these 5 studies, Effexor was shown to be significantly superior to placebo on at least 2 of the following 3 measures: Hamilton Depression Rating Scale (total score), Hamilton depressed mood item, and Clinical Global Impression-Severity of Illness rating. Doses from 75 to 225 mg/day were superior to placebo in outpatient studies and a mean dose of about 350 mg/day was effective in inpatients. Data from the 2 fixed-dose outpatient studies were suggestive of a dose-response relationship in the range of 75 to 225 mg/day. There was no suggestion of increased response with doses greater than 225 mg/day.

While there were no efficacy studies focusing specifically on an elderly population, elderly patients were included among the patients studied. Overall, approximately 2/3 of all patients in these trials were women. Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

In one longer-term study, adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on Effexor XR
(75, 150, or 225 mg, qAM) were randomized to continuation of their same Effexor XR dose or to placebo, for up to 26 weeks of observation for relapse. Response during the open phase was defined as a CGI Severity of Illness item score of ≤3 and a HAM-D-21 total score of ≤10 at the day 56 evaluation. Relapse during the double-blind phase was defined as follows: (1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of ≥4 (moderately ill), (2) 2 consecutive CGI Severity of Illness item scores of ≥4, or (3) a final CGI Severity of Illness item score of ≥4 for any patient who withdrew from the study for any reason. Patients receiving continued Effexor XR treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, adult outpatients meeting DSM-III-R criteria for major depression, recurrent type, who had responded (HAM-D-21 total score ≤12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAM-D-21 total score ≥20; (2) no more than 2 HAM-D-21 total scores >10; and (3) no single CGI Severity of Illness item score ≥4 (moderately ill)] during an initial 26 weeks of treatment on Effexor (100 to 200 mg/day, on a b.i.d. schedule) were randomized to continuation of their same Effexor dose or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity of Illness item score ≥4, was for up to 52 weeks. Patients receiving continued Effexor treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

INDICATIONS AND USAGE

Effexor (venlafaxine hydrochloride) is indicated for the treatment of major depressive disorder.

The efficacy of Effexor in the treatment of major depressive disorder was established in 6-week controlled trials of adult outpatients whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depression and in a 4-week controlled trial of inpatients meeting diagnostic criteria for major depression with melancholia (see **CLINICAL TRIALS**).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The efficacy of Effexor XR in maintaining an antidepressant response for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of Effexor in maintaining an antidepressant response in patients with recurrent depression who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial (see **CLINICAL TRIALS**). Nevertheless, the physician who elects to use Effexor/Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**).

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with Effexor,** for a description of the risks of discontinuation of Effexor).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Effexor should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Effexor is not approved for use in treating bipolar depression.

Potential for Interaction with Monoamine Oxidase Inhibitors
Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on Effexor, or who have recently had Effexor therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with a monoamine oxidase inhibitor, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. Therefore,

it is recommended that Effexor not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Effexor, at least 7 days should be allowed after stopping Effexor before starting an MAOI.

Sustained Hypertension

Venlafaxine treatment is associated with sustained increases in blood pressure in some patients. (1) In a premarketing study comparing three fixed doses of venlafaxine (75, 225, and 375 mg/day) and placebo, a mean increase in supine diastolic blood pressure (SDBP) of 7.2 mm Hg was seen in the 375 mg/day group at week 6 compared to essentially no changes in the 75 and 225 mg/day groups and a mean decrease in SDBP of 2.2 mm Hg in the placebo group. (2) An analysis for patients meeting criteria for sustained hypertension (defined as treatment-emergent SDBP ≥ 90 mm Hg *and* ≥ 10 mm Hg above baseline for 3 consecutive visits) revealed a dose-dependent increase in the incidence of sustained hypertension for venlafaxine:

Probability of Sustained Elevation in SDBP (Pool of Premarketing Venlafaxine Studies)	
Treatment Group	Incidence of Sustained Elevation in SDBP
Venlafaxine	
< 100 mg/day	3%
101-200 mg/day	5%
201-300 mg/day	7%
> 300 mg/day	13%
Placebo	2%

An analysis of the patients with sustained hypertension and the 19 venlafaxine patients who were discontinued from treatment because of hypertension (<1% of total venlafaxine-treated group) revealed that most of the blood pressure increases were in a modest range (10 to 15 mm Hg, SDBP). Nevertheless, sustained increases of this magnitude could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

PRECAUTIONS

General

Discontinuation of Treatment with Effexor

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials in major depressive disorder. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of Effexor, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Effexor. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION**).

Anxiety and Insomnia

Treatment-emergent anxiety, nervousness, and insomnia were more commonly reported for venlafaxine-treated patients compared to placebo-treated patients in a pooled analysis of short-term, double-blind, placebo-controlled depression studies:

	Venlafaxine	Placebo
Symptom	n = 1033	n = 609
Anxiety	6%	3%
Nervousness	13%	6%
Insomnia	18%	10%

Anxiety, nervousness, and insomnia led to drug discontinuation in 2%, 2%, and 3%, respectively, of the patients treated with venlafaxine in the Phase 2 and Phase 3 depression studies.

Changes in Weight

Adult Patients: A dose-dependent weight loss was noted in patients treated with venlafaxine for several weeks. A loss of 5% or more of body weight occurred in 6% of patients treated with venlafaxine compared with 1% of patients treated with placebo and 3% of patients treated with another antidepressant. However, discontinuation for weight loss associated with venlafaxine was uncommon (0.1% of venlafaxine-treated patients in the Phase 2 and Phase 3 depression trials).

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of Effexor and weight loss agents is not recommended. Effexor is not indicated for weight loss alone or in combination with other products.

Pediatric Patients: Weight loss has been observed in pediatric patients (ages 6-17) receiving Effexor XR. In a pooled analysis of four eight-week, double-blind, placebo-controlled, flexible dose outpatient trials for major depressive disorder (MDD) and generalized anxiety disorder (GAD), Effexor XR-treated patients lost an average of 0.45 kg (n = 333), while placebo-treated patients gained an average of 0.77 kg (n = 333). More patients treated with Effexor XR than with placebo experienced a weight loss of at least 3.5% in both the MDD and the GAD studies (18% of Effexor XR-treated patients vs. 3.6% of placebo-treated patients; $p<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (see **PRECAUTIONS, General,** *Changes in Appetite*).

The risks associated with longer-term Effexor XR use were assessed in an open-label study of children and adolescents who received Effexor XR for up to six months. The children and adolescents in the study had increases in weight that were less than expected based on data from age- and sex-matched peers. The difference between observed weight gain and expected weight gain was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Height

Pediatric Patients: During the eight-week placebo-controlled GAD studies, Effexor XR-treated patients (ages 6-17) grew an average of 0.3 cm (n = 122), while placebo-treated patients grew an average of 1.0 cm (n = 132); $p=0.041$. This difference in height increase was most notable in patients younger than twelve. During the eight-week placebo-controlled MDD studies, Effexor XR-treated patients grew an average of 0.8 cm (n = 146), while placebo-treated patients grew an average of 0.7 cm (n = 147). In the six-month open-label study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates and expected growth rates was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Appetite

Adult Patients: Treatment-emergent anorexia was more commonly reported for venlafaxine-treated (11%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled depression studies.

Pediatric Patients: Decreased appetite has been observed in pediatric patients receiving Effexor XR. In the placebo-controlled trials for GAD and MDD, 10% of patients aged 6-17 treated with Effexor XR for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving Effexor XR discontinued for anorexia or weight loss.

Activation of Mania/Hypomania

During Phase 2 and Phase 3 trials, hypomania or mania occurred in 0.5% of patients treated with venlafaxine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Effexor (venlafaxine hydrochloride) should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics.

Mydriasis

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.

Seizures

During premarketing testing, seizures were reported in 0.26% (8/3082) of venlafaxine-treated patients. Most seizures (5 of 8) occurred in patients receiving doses of 150 mg/day or less. Effexor should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Abnormal Bleeding

There have been reports of abnormal bleeding (most commonly ecchymosis) associated with venlafaxine treatment. While a causal relationship to venlafaxine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Serum Cholesterol Elevation

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see **ADVERSE REACTIONS–Laboratory Changes**). Measurement of serum cholesterol levels should be considered during long-term treatment.

Use in Patients with Concomitant Illness

Clinical experience with Effexor in patients with concomitant systemic illness is limited. Caution is advised in administering Effexor to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Effexor has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for 769 patients who received Effexor in 4- to 6-week double-blind placebo-controlled trials, however, showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo. The mean heart rate in Effexor-treated patients was increased relative to baseline by about 4 beats per minute.

The electrocardiograms for 357 patients who received Effexor XR (the extended-release form of venlafaxine) and 285 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials were analyzed. The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients was increased relative to that for placebo-treated patients (increase of 4.7 msec for Effexor XR and decrease of 1.9 msec for placebo). In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, Effexor-treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group.

As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (eg, patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when using doses of Effexor above 200 mg/day.

In patients with renal impairment (GFR=10 to 70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolite were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see **DOSAGE AND ADMINISTRATION**). Effexor (venlafaxine hydrochloride), like all antidepressants, should be used with caution in such patients.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Effexor. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Interference with Cognitive and Motor Performance
Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Effexor therapy does not adversely affect their ability to engage in such activities.

Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing
Patients should be advised to notify their physician if they are breast-feeding an infant.

Concomitant Medication
Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal preparations, since there is a potential for interactions.

Alcohol
Although Effexor has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Effexor.

Allergic Reactions
Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Laboratory Tests
There are no specific laboratory tests recommended.

Drug Interactions
As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Alcohol

A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or ODV when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

Cimetidine

Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, co-administration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than is venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

Diazepam

Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam.

Haloperidol

Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

Lithium

The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. O-desmethylvenlafaxine (ODV) also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium (see also *CNS-Active Drugs*, below).

Drugs Highly Bound to Plasma Protein

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Drugs that Inhibit Cytochrome P450 Isoenzymes

CYP2D6 Inhibitors: In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism and venlafaxine. However, although imipramine partially inhibited the CYP2D6-mediated metabolism of venlafaxine, resulting in higher plasma concentrations of venlafaxine and lower plasma concentrations of ODV, the total concentration of active compounds (venlafaxine plus ODV) was not affected. Additionally, in a clinical study involving CYP2D6-poor and -extensive metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the two metabolizer groups. Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

CYP3A4 Inhibitors: In vitro studies indicate that venlafaxine is likely metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. Because CYP3A4 is typically a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, the potential for a clinically significant drug interaction between drugs that inhibit CYP3A4-mediated metabolism and venlafaxine is small.

The concomitant use of venlafaxine with a drug treatment(s) that potently inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce potent simultaneous inhibition of these two enzyme systems.

Drugs Metabolized by Cytochrome P450 Isoenzymes

CYP2D6: In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine to that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Imipramine—Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Risperidone—Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

CYP3A4: Venlafaxine did not inhibit CYP3A4 in vitro. This finding was confirmed in vivo by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

Indinavir—In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

CYP1A2: Venlafaxine did not inhibit CYP1A2 in vitro. This finding was confirmed in vivo by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

CYP2C9: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the pharmacokinetics of a single 500 mg dose of tolbutamide or the CYP2C9 mediated formation of 4-hydroxy-tolbutamide.

CYP2C19: Venlafaxine did not inhibit the metabolism of diazepam which is partially metabolized by CYP2C19 (see *Diazepam* above).

Monoamine Oxidase Inhibitors
See **CONTRAINDICATIONS** and **WARNINGS**.

CNS-Active Drugs
The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated (except in the case of those CNS-active drugs noted above). Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required. Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when venlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors (SRIs), or lithium.

Electroconvulsive Therapy
There are no clinical data establishing the benefit of electroconvulsive therapy combined with Effexor treatment.

Postmarketing Spontaneous Drug Interaction Reports
See **ADVERSE REACTIONS, Postmarketing Reports**.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 16 times, on a mg/kg basis, and 1.7 times on a mg/m^2 basis, the maximum recommended human dose. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma levels of venlafaxine were 1 times (male rats) and 6 times (female rats) the plasma levels of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenicity

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic in the in vitro BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured CHO cells, or the in vivo chromosomal aberration assay in rat bone marrow. ODV was not mutagenic in the in vitro CHO cell chromosomal aberration assay. There was a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow in male rats receiving 200 times, on a mg/kg basis, or 50 times, on a mg/m^2 basis, the maximum human daily dose. The no effect dose was 67 times (mg/kg) or 17 times (mg/m^2) the human dose.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose on a mg/kg basis, or up to 2 times on a mg/m^2 basis.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the maximum recommended human daily dose on a mg/kg basis, or 2.5 times (rat) and 4 times (rabbit) the human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times (mg/kg) or 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 1.4 times the human dose on a mg/kg basis or 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects

Neonates exposed to Effexor, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **PRECAUTIONS-Drug Interactions-***CNS-Active Drugs*). When treating a pregnant woman with Effexor during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**).

Labor and Delivery

The effect of Effexor® (venlafaxine hydrochloride) on labor and delivery in humans is unknown.

Nursing Mothers

Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS, Clinical Worsening and Suicide Risk**). Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of Effexor in a child or adolescent must balance the potential risks with the clinical need.

Although no studies have been designed to primarily assess Effexor XR's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that Effexor XR may adversely affect weight and height (see **PRECAUTIONS, General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term. The safety of Effexor XR treatment for pediatric patients has not been systematically assessed for chronic treatment longer than six months in duration.

In the studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients (see **WARNINGS, Sustained Hypertension**, and **PRECAUTIONS, General**, *Serum Cholesterol Elevation*).

Geriatric Use

Of the 2,897 patients in Phase 2 and Phase 3 depression studies with Effexor, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see **CLINICAL PHARMACOLOGY**). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Nineteen percent (537/2897) of venlafaxine patients in Phase 2 and Phase 3 depression studies discontinued treatment due to an adverse event. The more common events (≥ 1%) associated with discontinuation and considered to be drug-related (ie, those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) included:

CNS	Venlafaxine	Placebo
Somnolence	3%	1%
Insomnia	3%	1%
Dizziness	3%	—
Nervousness	2%	—
Dry mouth	2%	—
Anxiety	2%	1%
Gastrointestinal		
Nausea	6%	1%
Urogenital		
Abnormal ejaculation*	3%	—
Other		
Headache	3%	1%
Asthenia	2%	—
Sweating	2%	—

* Percentages based on the number of males.
— Less than 1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

The most commonly observed adverse events associated with the use of Effexor® (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (ie, incidence for Effexor at least twice that for placebo), derived from the 1% incidence table below, were asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence in men.

Adverse Events Occurring at an Incidence of 1% or More Among Effexor-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Effexor-treated patients who participated in short-term (4- to 8-week) placebo-controlled trials in which patients were administered doses in a range of 75 to 375 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

TABLE 1
Treatment-Emergent Adverse Experience Incidence in 4- to 8-Week Placebo-Controlled Clinical Trials[1]

Body System	Preferred Term	Effexor (n=1033)	Placebo (n=609)
Body as a Whole	Headache	25%	24%
	Asthenia	12%	6%
	Infection	6%	5%
	Chills	3%	—
	Chest pain	2%	1%
	Trauma	2%	1%
Cardiovascular	Vasodilatation	4%	3%
	Increased blood pressure/hypertension	2%	—
	Tachycardia	2%	—
	Postural hypotension	1%	—
Dermatological	Sweating	12%	3%
	Rash	3%	2%
	Pruritus	1%	—
Gastrointestinal	Nausea	37%	11%
	Constipation	15%	7%
	Anorexia	11%	2%
	Diarrhea	8%	7%
	Vomiting	6%	2%
	Dyspepsia	5%	4%
	Flatulence	3%	2%
Metabolic	Weight loss	1%	—

Body System	Preferred Term	Effexor (n=1033)	Placebo (n=609)
Nervous System	Somnolence	23%	9%
	Dry mouth	22%	11%
	Dizziness	19%	7%
	Insomnia	18%	10%
	Nervousness	13%	6%
	Anxiety	6%	3%
	Tremor	5%	1%
	Abnormal dreams	4%	3%
	Hypertonia	3%	2%
	Paresthesia	3%	2%
	Libido decreased	2%	—
	Agitation	2%	—
	Confusion	2%	1%
	Thinking abnormal	2%	1%
	Depersonalization	1%	—
	Depression	1%	—
	Urinary retention	1%	—
	Twitching	1%	—
Respiration	Yawn	3%	—
Special Senses	Blurred vision	6%	2%
	Taste perversion	2%	—
	Tinnitus	2%	—
	Mydriasis	2%	—
Urogenital System	Abnormal ejaculation/ orgasm	12%[2]	—[2]
	Impotence	6%[2]	—[2]
	Urinary frequency	3%	2%
	Urination impaired	2%	—
	Orgasm disturbance	2%[3]	—[3]

[1] Events reported by at least 1% of patients treated with Effexor (venlafaxine hydrochloride) are included, and are rounded to the nearest %. Events for which the Effexor incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, flu syndrome, fever, palpitation, increased appetite, myalgia, arthralgia, amnesia, hypesthesia, rhinitis, pharyngitis, sinusitis, cough increased, and dysmenorrhea[3].

— Incidence less than 1%.

[2] Incidence based on number of male patients.

[3] Incidence based on number of female patients.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing Effexor (venlafaxine hydrochloride) 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with Effexor use, as shown in the table that follows. The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one Effexor group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value ≤ 0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

TABLE 2
Treatment-Emergent Adverse Experience Incidence in a Dose Comparison Trial

Body System/ Preferred Term	Effexor (mg/day) Placebo (n=92)	75 (n=89)	225 (n=89)	375 (n=88)
Body as a Whole				
Abdominal pain	3.3%	3.4%	2.2%	8.0%
Asthenia	3.3%	16.9%	14.6%	14.8%
Chills	1.1%	2.2%	5.6%	6.8%
Infection	2.2%	2.2%	5.6%	2.3%
Cardiovascular System				
Hypertension	1.1%	1.1%	2.2%	4.5%
Vasodilatation	0.0%	4.5%	5.6%	2.3%
Digestive System				
Anorexia	2.2%	14.6%	13.5%	17.0%
Dyspepsia	2.2%	6.7%	6.7%	4.5%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Nervous System				
Agitation	0.0%	1.1%	2.2%	4.5%
Anxiety	4.3%	11.2%	4.5%	2.3%
Dizziness	4.3%	19.1%	22.5%	23.9%
Insomnia	9.8%	22.5%	20.2%	13.6%
Libido decreased	1.1%	2.2%	1.1%	5.7%
Nervousness	4.3%	21.3%	13.5%	12.5%
Somnolence	4.3%	16.9%	18.0%	26.1%
Tremor	0.0%	1.1%	2.2%	10.2%
Respiratory System				
Yawn	0.0%	4.5%	5.6%	8.0%
Skin and Appendages				
Sweating	5.4%	6.7%	12.4%	19.3%
Special Senses				
Abnormality of accommodation	0.0%	9.1%	7.9%	5.6%
Urogenital System				
Abnormal ejaculation/orgasm	0.0%	4.5%	2.2%	12.5%
Impotence	0.0%	5.8%	2.1%	3.6%
(Number of men)	(n=63)	(n=52)	(n=48)	(n=56)

Adaptation to Certain Adverse Events

Over a 6-week period, there was evidence of adaptation to some adverse events with continued therapy (eg, dizziness and nausea), but less to other effects (eg, abnormal ejaculation and dry mouth).

Vital Sign Changes

Effexor (venlafaxine hydrochloride) treatment (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. In a flexible-dose study, with doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

In controlled clinical trials, Effexor was associated with mean increases in diastolic blood pressure ranging from 0.7 to 2.5 mm Hg averaged over all dose groups, compared to mean decreases ranging from 0.9 to 3.8 mm Hg for placebo. However, there is a dose dependency for blood pressure increase (see **WARNINGS**).

Laboratory Changes

Of the serum chemistry and hematology parameters monitored during clinical trials with Effexor, a statistically significant difference with placebo was seen only for serum cholesterol. In premarketing trials, treatment with Effexor tablets was associated with a mean final on-therapy increase in total cholesterol of 3 mg/dL.

Patients treated with Effexor tablets for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared with a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General-***Serum Cholesterol Elevation*).

ECG Changes

In an analysis of ECGs obtained in 769 patients treated with Effexor and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, ie, a mean increase from baseline of 4 beats per minute for Effexor. In a flexible-dose study, with doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo (see **PRECAUTIONS**, **General**, *Use in Patients with Concomitant Illness*).

Other Events Observed During the Premarketing Evaluation of Venlafaxine

During its premarketing assessment, multiple doses of Effexor were administered to 2897 patients in Phase 2 and Phase 3 studies. In addition, in premarketing assessment of Effexor XR (the extended release form of venlafaxine), multiple doses were administered to 705 patients in Phase 3 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were also administered to 1381 patients in Phase 3 GAD studies and 277 patients in Phase 3 Social Anxiety Disorder studies. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 5356 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Table 1 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: **frequent** adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients.

Body as a whole—**Frequent:** accidental injury, chest pain substernal, neck pain; **Infrequent:** face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; **Rare**: appendicitis, bacteremia, carcinoma, cellulitis.

Cardiovascular system—**Frequent:** migraine; **Infrequent:** angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cardiovascular disorder (mitral valve and circulatory disturbance), cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, mucocutaneous hemorrhage, myocardial infarct, pallor.

Digestive system—**Frequent:** eructation; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; **Rare:** cheilitis, cholecystitis, cholelithiasis, duodenitis, esophageal spasm, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, periodontitis, proctitis, increased salivation, soft stools, tongue discoloration.

Endocrine system—**Rare:** goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and lymphatic system—**Frequent:** ecchymosis; **Infrequent:** anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; **Rare:** basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura.

Metabolic and nutritional—**Frequent:** edema, weight gain; **Infrequent:** alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT (AST) increased, SGPT (ALT) increased, thirst; **Rare:** alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia.

Musculoskeletal system—**Infrequent:** arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** pathological fracture, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.

Nervous system—**Frequent:** trismus, vertigo; **Infrequent:** akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor; **Rare:** akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, feeling drunk, abnormal gait, Guillain-Barre Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis.

Respiratory system—**Frequent:** bronchitis, dyspnea; **Infrequent:** asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare:** atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea.

Skin and appendages—**Infrequent:** acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare:** erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, petechial rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae.

Special senses—**Frequent:** abnormality of accommodation, abnormal vision; **Infrequent:** cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis.

Urogenital system—**Frequent:** metrorrhagia*, prostatic disorder (prostatitis and enlarged prostate)*, vaginitis*; **Infrequent:** albuminuria, amenorrhea*, cystitis, dysuria, hematuria, leukorrhea*, menorrhagia*, nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary urgency, vaginal hemorrhage*; **Rare**: abortion*, anuria, balanitis*, breast discharge, breast engorgement, breast enlargement, endometriosis*, fibrocystic breast, calcium crystalluria, cervicitis*, ovarian cyst*, prolonged erection*, gynecomastia (male)*, hypomenorrhea*, kidney calculus, kidney pain, kidney function abnormal, female lactation*, mastitis, menopause*, oliguria, orchitis*, pyelonephritis, salpingitis*, urolithiasis, uterine hemorrhage*, uterine spasm*, vaginal dryness*.

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* Based on the number of men and women as appropriate.

Postmarketing Reports

Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystole, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsade de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Effexor (venlafaxine hydrochloride) is not a controlled substance.

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Discontinuation effects have been reported in patients receiving venlafaxine (see **DOSAGE AND ADMINISTRATION**).

While Effexor has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Effexor (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There were 14 reports of acute overdose with Effexor (venlafaxine hydrochloride), either alone or in combination with other drugs and/or alcohol, among the patients included in the premarketing evaluation. The majority of the reports involved ingestions in which the total dose of Effexor taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 μg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 μg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, and death have been reported.

Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR).*

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for Effexor is 75 mg/day, administered in two or three divided doses, taken with food. Depending on tolerability and the need for further clinical effect, the dose may be increased to 150 mg/day. If needed, the dose should be further increased up to 225 mg/day. When increasing the dose, increments of up to 75 mg/day should be made at intervals of no less than 4 days. In outpatient settings there was no evidence of usefulness of doses greater than 225 mg/day for moderately depressed patients, but more severely depressed inpatients responded to a mean dose of 350 mg/day. Certain patients, including more severely depressed patients, may therefore respond more to higher doses, up to a maximum of 375 mg/day, generally in three divided doses (see **PRECAUTIONS, General**, *Use in Patients with Concomitant Illness*).

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Effexor, other SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with Effexor during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Effexor in the third trimester.

Dosage for Patients with Hepatic Impairment

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared to normal subjects (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 50% in patients with moderate hepatic impairment. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Dosage for Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10 to 70 mL/min) compared to normals (see **CLINICAL PHARMACOLOGY**), it is recommended that the total daily dose be reduced by 25% in patients with mild to moderate renal impairment. It is recommended that the total daily dose be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hrs) in patients undergoing hemodialysis. Since there was much individual variability in clearance between patients with renal impairment, individualization of dosing may be desirable in some patients.

Dosage for Elderly Patients

No dose adjustment is recommended for elderly patients on the basis of age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining an antidepressant response in patients with recurrent depression who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or Effexor for periods of up to 52 weeks on the same dose (100 to 200 mg/day, on a b.i.d. schedule) (see **CLINICAL TRIALS**). Based on these limited data, it is not known whether or not the dose of Effexor/Effexor XR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Discontinuing Effexor (venlafaxine hydrochloride)

Symptoms associated with discontinuation of Effexor, other SNRIs, and SSRIs, have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor. In addition, at least 7 days should be allowed after stopping Effexor before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Effexor® (venlafaxine hydrochloride) Tablets are available as follows:

25 mg, peach, shield-shaped tablet with "25" and a "W" on one side and "701" on scored reverse side.

NDC 0008-0701-01, bottle of 100 tablets.

NDC 0008-0701-02, carton of 10 Redipak® blister strips of 10 tablets each.

37.5 mg, peach, shield-shaped tablet with "37.5" and a "W"on one side and "781" on scored reverse side.

NDC 0008-0781-01, bottle of 100 tablets.

NDC 0008-0781-02, carton of 10 Redipak® blister strips of 10 tablets each.

50 mg, peach, shield-shaped tablet with "50" and a "W" on one side and "703" on scored reverse side.

NDC 0008-0703-01, bottle of 100 tablets.

NDC 0008-0703-02, carton of 10 Redipak® blister strips of 10 tablets each.

75 mg, peach, shield-shaped tablet with "75" and a "W" on one side and "704" on scored reverse side.

NDC 0008-0704-01, bottle of 100 tablets.

NDC 0008-0704-02, carton of 10 Redipak® blister strips of 10 tablets each.

100 mg, peach, shield-shaped tablet with "100" and a "W" on one side and "705" on scored reverse side.

NDC 0008-0705-01, bottle of 100 tablets.

NDC 0008-0705-02, carton of 10 Redipak® blister strips of 10 tablets each.

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

Store at controlled room temperature 20° to 25°C (68° to 77°F) in a dry place.

Dispense in a well-closed container as defined in the USP.

Medication Guide
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions.
2. How to try to prevent suicidal thoughts or actions in your child.
3. You should watch for certain signs if your child is taking an antidepressant.
4. There are benefits and risks when using antidepressants.

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with:

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).*

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

* Prozac® is a registered trademark of Eli Lilly and Company
Zoloft® is a registered trademark of Pfizer Pharmaceuticals
Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

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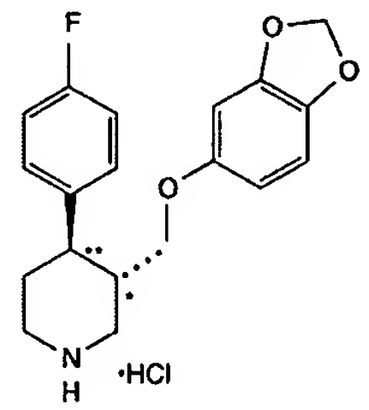
ET01
Rev 01/05

PRESCRIBING INFORMATION

PAXIL CR™
(paroxetine hydrochloride) Controlled-Release Tablets

DESCRIPTION

PAXIL CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic, or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \bullet HCl \bullet 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg–yellow, 25 mg–pink, 37.5 mg–blue. One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix.

Inactive ingredients consist of hypromellose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and 1 or more of the following colorants: Yellow ferric oxide, red ferric oxide, D&C Red No. 30, D&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics: The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak

effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha$_1$-, alpha$_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT_1-, 5-HT_2-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic, and alpha$_1$-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics: Tablets of PAXIL CR contain a degradable polymeric matrix (GEOMATRIX™) designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C_{max} and $AUC_{0\text{-}inf}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and $AUC_{0\text{-}inf}$ values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng•hr./mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The mean elimination half-life of paroxetine was 15 to 20 hours throughout this range of single doses of PAXIL CR. The bioavailability of 25 mg PAXIL CR is not affected by food.

During repeated administration of PAXIL CR (25 mg once daily), steady state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n = 23) received PAXIL CR (25 mg daily), mean steady state C_{max}, C_{min}, and $AUC_{0\text{-}24}$ values were 30 ng/mL, 20 ng/mL, and 550 ng•hr./mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on $AUC_{0\text{-}24}$ was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}IID_6$. Saturation of this enzyme at clinical doses appears

to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution: Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding: Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or warfarin.

Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min. was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients: In a multiple-dose study in the elderly at daily doses of 20, 30, and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Clinical Trials

Major Depressive Disorder: The efficacy of PAXIL CR controlled-release tablets as a treatment for major depressive disorder has been established in two 12-week, flexible-dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18 to 65 years, and a second study included elderly patients, ranging in age from 60 to 88. In both studies, PAXIL CR was shown to be significantly more effective than placebo in treating major depressive disorder as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)–Severity of Illness score.

A study of outpatients with major depressive disorder who had responded to immediate-release paroxetine tablets (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on immediate-release paroxetine tablets or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking immediate-release paroxetine tablets (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Panic Disorder: The effectiveness of PAXIL CR in the treatment of panic disorder was evaluated in three 10-week, multicenter, flexible-dose studies (Studies 1, 2, and 3) comparing paroxetine controlled-release (12.5 to 75 mg daily) to placebo in adult outpatients who had panic disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their outcomes on 3 variables: (1) the proportions of patients free of full panic attacks at endpoint; (2) change from baseline to endpoint in the median number of full panic attacks; and (3) change from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1 and 2, PAXIL CR was consistently superior to placebo on 2 of these 3 variables. Study 3 failed to consistently demonstrate a significant difference between PAXIL CR and placebo on any of these variables.

For all 3 studies, the mean dose of PAXIL CR for completers at endpoint was approximately 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Long-term maintenance effects of the immediate-release formulation of paroxetine in panic disorder were demonstrated in an extension study. Patients who were responders during a 10-week double-blind phase with immediate-release paroxetine and during a 3-month double-blind extension phase were randomized to either immediate-release paroxetine or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Social Anxiety Disorder: The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the effectiveness of PAXIL CR in the treatment of social anxiety disorder was demonstrated in a 12-week, multicenter, double-blind, flexible-dose, placebo-controlled study of adult outpatients with a primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of PAXIL CR (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1) change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the Clinical Global Impression (CGI) Global Improvement score.

PAXIL CR demonstrated statistically significant superiority over placebo on both the LSAS total score and the CGI Improvement responder criterion. For patients who completed the trial, 64% of patients treated with PAXIL CR compared to 34.7% of patients treated with placebo were CGI Improvement responders.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of paroxetine generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Premenstrual Dysphoric Disorder: The effectiveness of PAXIL CR for the treatment of PMDD utilizing a continuous dosing regimen has been established in 2 placebo-controlled trials.

Patients in these trials met DSM-IV criteria for PMDD. In a pool of 1,030 patients, treated with daily doses of PAXIL CR 12.5 or 25 mg/day, or placebo the mean duration of the PMDD symptoms was approximately 11 ± 7 years. Patients on systemic hormonal contraceptives were excluded from these trials. Therefore, the efficacy of PAXIL CR in combination with systemic (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is unknown. In both positive studies, patients (N = 672) were treated with 12.5 mg/day or 25 mg/day of PAXIL CR or placebo continuously throughout the menstrual cycle for a period of 3 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms. 12.5 mg/day and 25 mg/day of PAXIL CR were significantly more effective than placebo as measured by change from baseline to the endpoint on the luteal phase VAS-Total score.

In a third study employing intermittent dosing, patients (N = 366) were treated for the 2 weeks prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with 12.5 mg/day or 25 mg/day of PAXIL CR or placebo for a period of 3 months. 12.5 mg/day and 25 mg/day of PAXIL CR, as luteal phase dosing, was significantly more effective than placebo as measured by change from baseline luteal phase VAS total score.

There is insufficient information to determine the effect of race or age on outcome in these studies.

INDICATIONS AND USAGE

Major Depressive Disorder: PAXIL CR is indicated for the treatment of major depressive disorder.

The efficacy of PAXIL CR in the treatment of a major depressive episode was established in two 12-week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2-week period: Depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

PAXIL CR has not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to 1 year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY—Clinical Trials). The physician

who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Panic Disorder: PAXIL CR is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of PAXIL CR controlled-release tablets was established in two 10-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, the physician who prescribes PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Social Anxiety Disorder: PAXIL CR is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the efficacy of PAXIL CR was established in a 12-week trial, in adult outpatients with social anxiety disorder (DSM-IV). PAXIL CR has not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY—Clinical Trials).

The effectiveness of PAXIL CR in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Premenstrual Dysphoric Disorder: PAXIL CR is indicated for the treatment of PMDD.

The efficacy of PAXIL CR in the treatment of PMDD has been established in 3 placebo-controlled trials (see CLINICAL PHARMACOLOGY—Clinical Trials).

The essential features of PMDD, according to DSM-IV, include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following the onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of PAXIL CR in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

PAXIL CR is contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in PAXIL CR.

WARNINGS

Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that PAXIL CR not be used in

combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping PAXIL CR before starting an MAOI.

Potential Interaction With Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes–type arrhythmias, and sudden death. This effect appears to be dose related.

An in vivo study suggests that drugs which inhibit $P_{450}IID_6$, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Clinical Worsening and Suicide Risk: Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report

such symptoms immediately to health care providers. Prescriptions for PAXIL CR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment With PAXIL CR, for a description of the risks of discontinuation of PAXIL CR).

It should be noted that PAXIL CR is not approved for use in treating any indications in the pediatric population.

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that PAXIL CR is not approved for use in treating bipolar depression.

PRECAUTIONS

General: ***Activation of Mania/Hypomania:*** During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, PAXIL CR should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received PAXIL CR in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, 1 patient (0.1%) experienced a seizure. PAXIL CR should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment With PAXIL CR: Adverse events while discontinuing therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day,

spontaneously reported adverse events while discontinuing therapy with PAXIL CR were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for PAXIL CR, at an incidence of 2% or greater for PAXIL CR and were at least twice that reported for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR.

During marketing of PAXIL CR and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with PAXIL CR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Hyponatremia: Several cases of hyponatremia have been reported with immediate-release paroxetine hydrochloride. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Abnormal Bleeding: Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see Drug Interactions). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

Use in Patients With Concomitant Illness: Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution

is advisable in using PAXIL CR in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when PAXIL CR is prescribed for patients with narrow angle glaucoma.

PAXIL CR or the immediate-release formulation has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe PAXIL CR:

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference With Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies immediate-release paroxetine hydrochloride has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with PAXIL CR does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with use of PAXIL CR in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medications: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Although immediate-release paroxetine hydrochloride has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL CR.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant (see PRECAUTIONS—Nursing Mothers).

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: ***Tryptophan:*** As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of PAXIL CR with tryptophan is not recommended.

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of PAXIL CR and warfarin should be undertaken with caution (see Drugs That Interfere With Hemostasis).

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine: Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of PAXIL CR after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital: Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of

paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment with PAXIL CR is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin: When a single oral 30-mg dose of immediate-release paroxetine was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when PAXIL CR is coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS—Postmarketing Reports).

Drugs Metabolized by Cytochrome $P_{450}IID_6$: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P_{450} isozyme $P_{450}IID_6$. Like other agents that are metabolized by $P_{450}IID_6$, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this $P_{450}IID_6$ isozyme is saturated early during paroxetine dosing. In 1 study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of PAXIL CR with other drugs metabolized by cytochrome $P_{450}IID_6$ has not been formally studied but may require lower doses than usually prescribed for either PAXIL CR or the other drug.

Therefore, coadministration of PAXIL CR with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes that, unlike $P_{450}IID_6$, show no evidence of saturation (see PRECAUTIONS—Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome $P_{450}IIIA_4$: An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for $P_{450}IIIA_4$, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of $P_{450}IIIA_4$ activity, to be at least 100 times

more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's in vitro K_i and its lack of effect on terfenadine's in vivo clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration of TCAs with PAXIL CR, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with PAXIL CR (see PRECAUTIONS—Drugs Metabolized by Cytochrome $P_{450}IID_6$).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of PAXIL CR to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL CR.

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, since there is little clinical experience, the concurrent administration of PAXIL CR and lithium should be undertaken with caution.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of PAXIL CR and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of immediate-release paroxetine (30 mg once daily) increased steady-state $AUC_{0\text{-}24}$, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The

effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS—Postmarketing Reports).

Theophylline: Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and PAXIL CR.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 in vitro and 2 in vivo assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m^2 basis).

Pregnancy: Pregnancy Category C. Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors). When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

Labor and Delivery: The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when PAXIL CR is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see WARNINGS—Clinical Worsening and Suicide Risk).

Geriatric Use: In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, PAXIL CR was demonstrated to be safe and effective in the treatment of elderly patients (>60 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY—Clinical Trials and ADVERSE REACTIONS—Table 2.)

ADVERSE REACTIONS

The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR" subsection of ADVERSE REACTIONS is based on data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was conducted in patients with social anxiety disorder, and 4 studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. Information on additional adverse events associated with PAXIL CR and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR:

Adverse Events Associated With Discontinuation of Treatment: *Major Depressive Disorder:* Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for PAXIL CR compared to placebo) included the following:

	PAXIL CR (n = 212)	**Placebo (n = 211)**
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n = 104)	**Placebo (n = 109)**
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Panic Disorder: Eleven percent (50/444) of patients treated with PAXIL CR in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n = 444)	**Placebo (n = 445)**
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

Social Anxiety Disorder: Three percent (5/186) of patients treated with PAXIL CR in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n = 186)	**Placebo (n = 184)**
Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

Premenstrual Dysphoric Disorder: Spontaneously reported adverse events were monitored in studies of both continuous and intermittent dosing of PAXIL CR in the treatment of PMDD. Generally, there were few differences in the adverse event profiles of the 2 dosing regimens. Thirteen percent (88/681) of patients treated with PAXIL CR in PMDD studies of continuous dosing discontinued treatment due to an adverse event.

The most common events (≥1%) associated with discontinuation in either group treated with PAXIL CR with an incidence rate that is at least twice that of placebo in PMDD trials that employed a continuous dosing regimen are shown in the following table. This table also shows those events that were dose dependent (indicated with an asterisk) as defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
TOTAL	15%	9.9%	6.3%
Nausea*	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration Impaired*	2.0%	0.6%	0.3%
Dry mouth*	2.0%	0.6%	0.3%
Dizziness*	1.7%	0.6%	0.6%
Decreased Appetite*	1.4%	0.6%	0.0%
Sweating*	1.4%	0.0%	0.3%
Tremor*	1.4%	0.3%	0.0%
Yawn*	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

* Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

Commonly Observed Adverse Events: *Major Depressive Disorder:*

The most commonly observed adverse events associated with the use of PAXIL CR in a pool of 2 trials (incidence of 5.0% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 1) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of PAXIL CR in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder: In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder: In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder: The most commonly observed adverse events associated with the use of PAXIL CR either during continuous dosing or luteal phase dosing (incidence of 5% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 5) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation.

In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the 3 off-drug phases were combined, the following adverse events were reported at an incidence of 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo: Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%), sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

Incidence in Controlled Clinical Trials: Table 1 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 2 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 3 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day. Table 5 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR who participated in three, 12-week, placebo-controlled trials in PMDD in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With PAXIL CR in a Pool of 2 Studies in Major Depressive Disorder1,2

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 212)**	**Placebo (n = 211)**
Body as a Whole		

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 212)**	**Placebo (n = 211)**
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[9,10]	26%	1%

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 212)**	**Placebo (n = 211)**
Female Genital Disorder[9,11]	10%	<1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[9]	2%	<1%
Vaginitis[9]	2%	0%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. <1% means greater than zero and less than 1%.
3. Mostly flu.
4. A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients Treated With PAXIL CR in a Study of Elderly Patients With Major Depressive Disorder1,2

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 104)**	**Placebo (n = 109)**
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%

Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
2. <1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With PAXIL CR in a Pool of 3 Panic Disorder Studies1,2

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 444)**	**Placebo (n = 445)**
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 444)	Placebo (n = 445)
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	<1%
Urogenital System		
Abnormal Ejaculation[7,8]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[9,10]	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis[9]	1%	<1%

1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Mostly flushing.
5. Mostly muscle tightness or stiffness.
6. Mostly blurred vision.
7. Based on the number of male patients.
8. Mostly anorgasmia or delayed ejaculation.
9. Based on the number of female patients.
10. Mostly anorgasmia or difficulty achieving orgasm.

Table 4. Treatment-Emergent Adverse Effects Occurring in ≥1% of Patients Treated With PAXIL CR in a Social Anxiety Disorder Study1,2

	% Reporting Event

Body System/Adverse Event	PAXIL CR (n = 186)	Placebo (n = 184)
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back Pain	4%	1%
Trauma[3]	3%	<1%
Allergic Reaction[4]	2%	<1%
Chest Pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%
Dyspepsia	2%	<1%
Decreased Appetite	1%	<1%
Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight Gain	3%	1%
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal Vision[5]	2%	0%
Abnormality of	2%	0%

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 186)**	**Placebo (n = 184)**
Accommodation		
Urogenital System		
Abnormal Ejaculation[6,7]	15%	1%
Impotence[6]	9%	0%
Female Genital Disorders[8,9]	3%	0%

1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Most frequently seasonal allergic symptoms.
5. Mostly blurred vision.
6. Based on the number of male patients.
7. Mostly anorgasmia or delayed ejaculation.
8. Based on the number of female patients.
9. Mostly anorgasmia or difficulty achieving orgasm.

Table 5. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies with Continuous Dosing or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing[1,2,3]

	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
Body System/Adverse Event	**PAXIL CR (n = 681)**	**Placebo (n = 349)**	**PAXIL CR (n = 246)**	**Placebo (n = 120)**
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	-	-
Infection	6%	4%	-	-
Abdominal pain	-	-	3%	0%
Cardiovascular System				
Migraine	1%	<1%	-	-
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry Mouth	4%	2%	2%	<1%
Increased Appetite	3%	<1%	-	-
Decreased Appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	-	-	1%	0%
Metabolic and Nutritional Disorders				
Generalized Edema	-	-	1%	<1%
Weight Gain	-	-	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	-	-
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration Impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	-	-
Lack of Emotion	2%	<1%	-	-
Depression	-	-	2%	<1%
Vertigo	-	-	2%	<1%
Abnormal Dreams	1%	<1%	-	-
Amnesia	-	-	1%	0%
Respiratory System				
Sinusitis	-	-	4%	2%

Body System/Adverse Event	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
	PAXIL CR (n = 681)	Placebo (n = 349)	PAXIL CR (n = 246)	Placebo (n = 120)
Yawn	2%	<1%	-	-
Bronchitis	-	-	2%	0%
Cough Increased	1%	<1%	-	-
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal Vision	-	-	1%	0%
Urogenital System				
Female Genital Disorders[4]	8%	1%	2%	0%
Menorrhagia	1%	<1%	-	-
Vaginal Moniliasis	1%	<1%	-	-
Menstrual Disorder	-	-	1%	0%

1. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the placebo rate are not included. These events for continuous dosing are: Abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis, pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma, myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
2. <1% means greater than zero and less than 1%.
3. The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing regimens of the PMDD trials of incidence rates shown in Table 5 should be avoided.
4. Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependency of Adverse Events: The following table shows results in PMDD trials of common adverse events, defined as events with an incidence of ≥1% with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR and with placebo.

Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
Common Adverse Event			
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%

Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

A comparison of adverse event rates in a fixed-dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

Male and Female Sexual Dysfunction With SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain; however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled continuous dosing trials in female patients with PMDD are as follows:

	Major Depressive Disorder		**Panic Disorder**		**Social Anxiety Disorder**		**PMDD Continuous Dosing**		**PMDD Luteal Phase Dosing**	
	PAXIL CR	**Placebo**	**PAXIL CR**	**Placebo**	**PAXIL CR**	**Placebo**	**PAXIL CR**	**Placebo**	**PAXIL CR**	**Placebo**
n (males)	**78**	**78**	**162**	**194**	**88**	**97**	**n/a**	**n/a**	**n/a**	**n/a**
Decreased Libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	**134**	**133**	**282**	**251**	**98**	**87**	**681**	**349**	**246**	**120**
Decreased Libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasmic Disturbance	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with PAXIL CR, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In a pool of 2 placebo-controlled clinical trials, patients treated with PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all 4 patients decreased substantially after discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Other Events Observed During the Clinical Development of Paroxetine: The following adverse events were reported during the clinical development of PAXIL CR and/or the clinical development of the immediate-release formulation of paroxetine.

Adverse events for which frequencies are provided below occurred in clinical trials with the controlled-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder, social anxiety disorder, and PMDD multiple doses of PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators

using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1 occasion while receiving PAXIL CR. All reported events are included except those already listed in Tables 1 through 5 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included. The extent to which these events may be associated with PAXIL CR is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis,

glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*, nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Postmarketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome–like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor); status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: PAXIL CR is not a controlled substance.

Physical and Psychologic Dependence: PAXIL CR has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to

which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of PAXIL CR (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS—Drugs Metabolized by Cytochrome $P_{450}IID_6$).

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder: *Usual Initial Dosage:* PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg, which corresponds to a 37.5-mg dose of PAXIL CR, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY—Pharmacokinetics).

Panic Disorder: *Usual Initial Dosage:* PAXIL CR should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR. The maximum dosage should not exceed 75 mg/day.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Anxiety Disorder: ***Usual Initial Dosage:*** PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with PAXIL CR should remain on it. Although the efficacy of PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Premenstrual Dysphoric Disorder: ***Usual Initial Dosage:*** PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. PAXIL CR may be administered either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. The recommended initial dose is 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance/Continuation Therapy: The effectiveness of PAXIL CR for a period exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients should be periodically reassessed to determine the need for continued treatment.

Special Populations*: Treatment of Pregnant Women During the Third Trimester:* Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or Hepatic Impairment: The recommended initial dose of PAXIL CR is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or From a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL CR. Similarly, at least 14 days should be allowed after stopping PAXIL CR before starting an MAOI.

Discontinuation of Treatment With PAXIL CR: Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

PAXIL CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

12.5-mg yellow tablets, engraved with Paxil CR and 12.5

NDC 0029-3206-13 Bottles of 30

NDC 0029-3206-20 Bottles of 100

25-mg pink tablets, engraved with Paxil CR and 25

NDC 0029-3207-13 Bottles of 30

NDC 0029-3207-20 Bottles of 100

NDC 0029-3207-21 SUP 100s (intended for institutional use only)

37.5-mg blue tablets, engraved with Paxil CR and 37.5

NDC 0029-3208-13 Bottles of 30

Store at or below 25°C (77°F) [see USP].

PAXIL CR is a trademark of GlaxoSmithKline.

GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.

GlaxoSmithKline
Research Triangle Park, NC 27709

April 2004 PC:L10

ZOLOFT®
(sertraline hydrochloride)
Tablets and Oral Concentrate

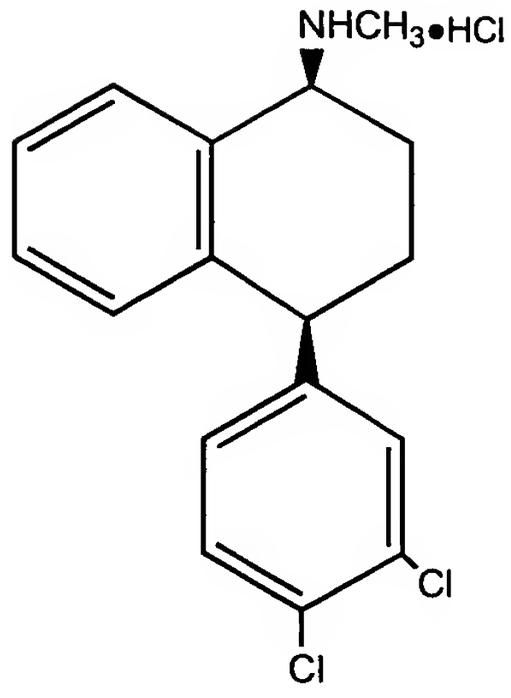
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See Warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2 \bullet HCl$ is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25 mg tablet), FD & C Blue #1 aluminum lake (in 25 mg tablet), FD & C Red #40 aluminum lake (in 25 mg tablet), FD & C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide.

ZOLOFT oral concentrate is available in a multidose 60 mL bottle. Each mL of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT). The oral concentrate must be diluted prior to administration (see PRECAUTIONS, Information for Patients and DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic ($alpha_1$, $alpha_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability–In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and Cmax values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80-125% with the exception of the upper 90% CI limit for Cmax which was 126.5%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 5.9 hours to 7.0 hours with food.

Metabolism–Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction,

hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), Cmax and Cmin, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein Binding–*In vitro* protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see PRECAUTIONS).

Pediatric Pharmacokinetics–Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6-12 year old group exhibited a mean sertraline AUC (0-24 hr) of 3107 ng-hr/mL, mean Cmax of 165 ng/mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng-hr/mL, mean Cmax of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0-24 hr) of 2570 ng-hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 year olds showed about 22% lower AUC (0-24 hr) and Cmax values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels (see DOSAGE AND ADMINISTRATION).

Age–Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.

Liver Disease–As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who

received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease–Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr=30-60 mL/min), moderate to severe (CLcr=10-29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment (see PRECAUTIONS).

Clinical Trials

Major Depressive Disorder–The efficacy of ZOLOFT as a treatment for major depressive disorder was established in two placebo-controlled studies in adult outpatients meeting DSM-III criteria for major depressive disorder. Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 145 mg/day. Study 2 was a 6-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Overall, these studies demonstrated ZOLOFT to be superior to placebo on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement scales. Study 2 was not readily interpretable regarding a dose response relationship for effectiveness.

Study 3 involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on ZOLOFT 50-200 mg/day. These patients (N=295) were randomized to continuation for 44 weeks on double-blind ZOLOFT 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking ZOLOFT compared to those on placebo. The mean dose for completers was 70 mg/day.

Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.

Obsessive-Compulsive Disorder (OCD)–The effectiveness of ZOLOFT in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had moderate to severe OCD (DSM-III or DSM-III-R) with mean baseline ratings on the Yale–Brown Obsessive-Compulsive Scale (YBOCS) total score ranging from 23 to 25.

Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 186 mg/day. Patients receiving ZOLOFT experienced a mean

reduction of approximately 4 points on the YBOCS total score which was significantly greater than the mean reduction of 2 points in placebo-treated patients.

Study 2 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT doses of 50 and 200 mg/day experienced mean reductions of approximately 6 points on the YBOCS total score which were significantly greater than the approximately 3 point reduction in placebo-treated patients.

Study 3 was a 12-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 185 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

The effectiveness of ZOLOFT for the treatment of OCD was also demonstrated in a 12-week, multicenter, placebo-controlled, parallel group study in a pediatric outpatient population (children and adolescents, ages 6-17). Patients receiving ZOLOFT in this study were initiated at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-17), and then titrated over the next four weeks to a maximum dose of 200 mg/day, as tolerated. The mean dose for completers was 178 mg/day. Dosing was once a day in the morning or evening. Patients in this study had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) total score of 22. Patients receiving sertraline experienced a mean reduction of approximately 7 units on the CYBOCS total score which was significantly greater than the 3 unit reduction for placebo patients. Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

In a longer-term study, patients meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on ZOLOFT 50-200 mg/day (n=224) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Response during the single-blind phase was defined as a decrease in the YBOCS score of ≥ 25% compared to baseline and a CGI-I of 1 (very much improved), 2 (much improved) or 3 (minimally improved). Relapse during the double-blind phase was defined as the following conditions being met (on three consecutive visits for 1 and 2, and for visit 3 for condition 3): (1) YBOCS score increased by ≥ 5 points, to a minimum of 20, relative to baseline; (2) CGI-I increased by ≥ one point; and (3) worsening of the patient's condition in the investigator's judgment, to justify alternative treatment. Insufficient clinical response indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Patients receiving continued ZOLOFT treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Panic Disorder–The effectiveness of ZOLOFT in the treatment of panic disorder was demonstrated in three double-blind, placebo-controlled studies (Studies 1-3) of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R), with or without agoraphobia.

Studies 1 and 2 were 10-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and then patients were dosed in a range of 50-200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT doses for completers to 10 weeks were 131 mg/day and 144 mg/day, respectively, for Studies 1 and 2. In these studies, ZOLOFT was shown to be significantly more effective than placebo on change from baseline in panic attack frequency and on the Clinical Global Impression Severity of Illness and Global Improvement scores. The difference between ZOLOFT and placebo in reduction from baseline in the number of full panic attacks was approximately 2 panic attacks per week in both studies.

Study 3 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT experienced a significantly greater reduction in panic attack frequency than patients receiving placebo. Study 3 was not readily interpretable regarding a dose response relationship for effectiveness.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age, race, or gender.

In a longer-term study, patients meeting DSM-III-R criteria for Panic Disorder who had responded during a 52-week open trial on ZOLOFT 50-200 mg/day (n=183) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Response during the open phase was defined as a CGI-I score of 1(very much improved) or 2 (much improved). Relapse during the double-blind phase was defined as the following conditions being met on three consecutive visits: (1) CGI-I $\geq$ 3; (2) meets DSM-III-R criteria for Panic Disorder; (3) number of panic attacks greater than at baseline. Insufficient clinical response indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Patients receiving continued ZOLOFT treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Posttraumatic Stress Disorder (PTSD)–The effectiveness of ZOLOFT in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies 1-2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies 1 and 2 combined) and 44% of patients (169 of the 385 patients treated) had secondary depressive disorder.

Studies 1 and 2 were 12-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and patients were then dosed in the range of 50-200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT dose for completers was 146 mg/day and 151 mg/day, respectively for Studies 1 and 2. Study outcome was assessed by the Clinician-Administered PTSD Scale Part 2 (CAPS) which is a multi-item instrument that

measures the three PTSD diagnostic symptom clusters of reexperiencing/intrusion, avoidance/numbing, and hyperarousal as well as the patient-rated Impact of Event Scale (IES) which measures intrusion and avoidance symptoms. ZOLOFT was shown to be significantly more effective than placebo on change from baseline to endpoint on the CAPS, IES and on the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. In two additional placebo-controlled PTSD trials, the difference in response to treatment between patients receiving ZOLOFT and patients receiving placebo was not statistically significant. One of these additional studies was conducted in patients similar to those recruited for Studies 1 and 2, while the second additional study was conducted in predominantly male veterans.

As PTSD is a more common disorder in women than men, the majority (76%) of patients in these trials were women (152 and 139 women on sertraline and placebo versus 39 and 55 men on sertraline and placebo; Studies 1 and 2 combined). Post hoc exploratory analyses revealed a significant difference between ZOLOFT and placebo on the CAPS, IES and CGI in women, regardless of baseline diagnosis of comorbid major depressive disorder, but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on ZOLOFT 50-200 mg/day (n=96) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for relapse. Response during the open phase was defined as a CGI-I of 1 (very much improved) or 2 (much improved), and a decrease in the CAPS-2 score of $> 30\%$ compared to baseline. Relapse during the double-blind phase was defined as the following conditions being met on two consecutive visits: (1) CGI-I ≥ 3; (2) CAPS-2 score increased by $\geq 30\%$ and by ≥ 15 points relative to baseline; and (3) worsening of the patient's condition in the investigator's judgment. Patients receiving continued ZOLOFT treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Premenstrual Dysphoric Disorder (PMDD) – The effectiveness of ZOLOFT for the treatment of PMDD was established in two double-blind, parallel group, placebo-controlled flexible dose trials (Studies 1 and 2) conducted over 3 menstrual cycles. Patients in Study 1 met DSM-III-R criteria for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as Premenstrual Dysphoric Disorder (PMDD) in DSM-IV. Patients in Study 2 met DSM-IV criteria for PMDD. Study 1 utilized daily dosing throughout the study, while Study 2 utilized luteal phase dosing for the 2 weeks prior to the onset of menses. The mean duration of PMDD symptoms for these patients was approximately 10.5 years in both studies. Patients on oral contraceptives were excluded from these trials; therefore, the efficacy of sertraline in combination with oral contraceptives for the treatment of PMDD is unknown.

Efficacy was assessed with the Daily Record of Severity of Problems (DRSP), a patient-rated instrument that mirrors the diagnostic criteria for PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms. Other efficacy

assessments included the Hamilton Depression Rating Scale (HAMD-17), and the Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scores.

In Study 1, involving n=251 randomized patients, ZOLOFT treatment was initiated at 50 mg/day and administered daily throughout the menstrual cycle. In subsequent cycles, patients were dosed in the range of 50-150 mg/day on the basis of clinical response and toleration. The mean dose for completers was 102 mg/day. ZOLOFT administered daily throughout the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the DRSP total score, the HAMD-17 total score, and the CGI-S score, as well as the CGI-I score at endpoint.

In Study 2, involving n=281 randomized patients, ZOLOFT treatment was initiated at 50 mg/day in the late luteal phase (last 2 weeks) of each menstrual cycle and then discontinued at the onset of menses. In subsequent cycles, patients were dosed in the range of 50-100 mg/day in the luteal phase of each cycle, on the basis of clinical response and toleration. Patients who were titrated to 100 mg/day received 50 mg/day for the first 3 days of the cycle, then 100 mg/day for the remainder of the cycle. The mean ZOLOFT dose for completers was 74 mg/day. ZOLOFT administered in the late luteal phase of the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the DRSP total score and the CGI-S score, as well as the CGI-I score at endpoint.

There was insufficient information to determine the effect of race or age on outcome in these studies.

Social Anxiety Disorder – The effectiveness of ZOLOFT in the treatment of social anxiety disorder (also known as social phobia) was established in two multicenter placebo-controlled studies (Study 1 and 2) of adult outpatients who met DSM-IV criteria for social anxiety disorder.

Study 1 was a 12-week, multicenter, flexible dose study comparing ZOLOFT (50-200 mg/day) to placebo, in which ZOLOFT was initiated at 25 mg/day for the first week. Study outcome was assessed by (a) the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician administered instrument that measures fear, anxiety and avoidance of social and performance situations, and by (b) the proportion of responders as defined by the Clinical Global Impression of Improvement (CGI-I) criterion of CGI-I $\leq$ 2 (very much or much improved). ZOLOFT was statistically significantly more effective than placebo as measured by the LSAS and the percentage of responders.

Study 2 was a 20-week, multicenter, flexible dose study that compared ZOLOFT (50-200 mg/day) to placebo. Study outcome was assessed by the (a) Duke Brief Social Phobia Scale (BSPS), a multi-item clinician-rated instrument that measures fear, avoidance and physiologic response to social or performance situations, (b) the Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS), a 5-item patient-rated instrument that measures change in the severity of phobic avoidance and distress, and (c) the CGI-I responder criterion of $\leq$ 2. ZOLOFT was shown to be statistically significantly more effective than placebo as measured by the BSPS total score

and fear, avoidance and physiologic factor scores, as well as the FQ-SPS total score, and to have significantly more responders than placebo as defined by the CGI-I.

Subgroup analyses did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-IV criteria for social anxiety disorder who had responded while assigned to ZOLOFT (CGI-I of 1 or 2) during a 20-week placebo-controlled trial on ZOLOFT 50-200 mg/day were randomized to continuation of ZOLOFT or to substitution of placebo for up to 24 weeks of observation for relapse. Relapse was defined as ≥ 2 point increase in the Clinical Global Impression – Severity of Illness (CGI-S) score compared to baseline or study discontinuation due to lack of efficacy. Patients receiving ZOLOFT continuation treatment experienced a statistically significantly lower relapse rate over this 24-week study than patients randomized to placebo substitution.

INDICATIONS AND USAGE

Major Depressive Disorder–ZOLOFT® (sertraline hydrochloride) is indicated for the treatment of major depressive disorder in adults.

The efficacy of ZOLOFT in the treatment of a major depressive episode was established in six to eight week controlled trials of adult outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of ZOLOFT in hospitalized depressed patients has not been adequately studied.

The efficacy of ZOLOFT in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-Compulsive Disorder–ZOLOFT is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of ZOLOFT was established in 12-week trials with obsessive-compulsive outpatients having diagnoses of obsessive-compulsive disorder as defined according to DSM-III or DSM-III-R criteria (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The efficacy of ZOLOFT in maintaining a response, in patients with OCD who responded during a 52-week treatment phase while taking ZOLOFT and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see Clinical Trials under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder–ZOLOFT is indicated for the treatment of panic disorder in adults, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of ZOLOFT was established in three 10-12 week trials in adult panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The efficacy of ZOLOFT in maintaining a response, in adult patients with panic disorder who responded during a 52-week treatment phase while taking ZOLOFT and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see Clinical Trials under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Posttraumatic Stress Disorder (PTSD)–ZOLOFT (sertraline hydrochloride) is indicated for the treatment of posttraumatic stress disorder in adults.

The efficacy of ZOLOFT in the treatment of PTSD was established in two 12-week placebo-controlled trials of adult outpatients whose diagnosis met criteria for the DSM-III-R category of PTSD (see Clinical Trials under CLINICAL PHARMACOLOGY).

PTSD, as defined by DSM-III-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of ZOLOFT in maintaining a response in adult patients with PTSD for up to 28 weeks following 24 weeks of open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Premenstrual Dysphoric Disorder (PMDD) – ZOLOFT is indicated for the treatment of premenstrual dysphoric disorder (PMDD) in adults.

The efficacy of ZOLOFT in the treatment of PMDD was established in 2 placebo-controlled trials of female adult outpatients treated for 3 menstrual cycles who met criteria for the DSM-III-R/IV category of PMDD (see Clinical Trials under CLINICAL PHARMACOLOGY).

The essential features of PMDD include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of ZOLOFT in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Social Anxiety Disorder – ZOLOFT (sertraline hydrochloride) is indicated for the treatment of social anxiety disorder, also known as social phobia in adults.

The efficacy of ZOLOFT in the treatment of social anxiety disorder was established in two placebo-controlled trials of adult outpatients with a diagnosis of social anxiety disorder as defined by DSM-IV criteria (see Clinical Trials under CLINICAL PHARMACOLOGY).

Social anxiety disorder, as defined by DSM-IV, is characterized by marked and persistent fear of social or performance situations involving exposure to unfamiliar people or possible scrutiny by others and by fears of acting in a humiliating or embarrassing way. Exposure to the feared social situation almost always provokes anxiety and feared social or performance situations are avoided or else are endured with intense anxiety or distress. In addition, patients recognize that the fear is excessive or unreasonable and the avoidance and anticipatory anxiety of the feared situation is associated with functional impairment or marked distress.

The efficacy of ZOLOFT in maintaining a response in adult patients with social anxiety disorder for up to 24 weeks following 20 weeks of ZOLOFT treatment was demonstrated in a placebo-controlled trial. Physicians who prescribe ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Clinical Trials under CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

All Dosage Forms of ZOLOFT:
Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

ZOLOFT is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in ZOLOFT.

Oral Concentrate:
ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

WARNINGS

Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT® (sertraline hydrochloride), a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials**. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with ZOLOFT, for a description of the risks of discontinuation of ZOLOFT).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that ZOLOFT is not approved for use in treating bipolar depression.

PRECAUTIONS

General

Activation of Mania/Hypomania–During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT® (sertraline hydrochloride) treated patients.

Weight Loss–Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure–ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with ZOLOFT in the development program for major depressive disorder. However, 4 patients out of approximately 1800 (220<18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, ZOLOFT should be introduced with care in patients with a seizure disorder.

Discontinuation of Treatment with Zoloft

During marketing of Zoloft and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Zoloft. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a non-selective nonsteroidal anti-inflammatory drug (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies

focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of ZOLOFT with non-selective NSAIDs (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2), aspirin, or other drugs that affect coagulation.

Weak Uricosuric Effect–ZOLOFT® (sertraline hydrochloride) is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients with Concomitant Illness–Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities.

ZOLOFT administered in a flexible dose range of 50 to 200 mg/day (mean dose of 89 mg/day) was evaluated in a post-marketing, placebo-controlled trial of 372 randomized subjects with a DSM-IV diagnosis of major depressive disorder and recent history of myocardial infarction or unstable angina requiring hospitalization. Exclusions from this trial included, among others, patients with uncontrolled hypertension, need for cardiac surgery, history of CABG within 3 months of index event, severe or symptomatic bradycardia, non-atherosclerotic cause of angina, clinically significant renal impairment (creatinine > 2.5 mg/dl), and clinically significant hepatic dysfunction. ZOLOFT treatment initiated during the acute phase of recovery (within 30 days post-MI or post-hospitalization for unstable angina) was indistinguishable from placebo in this study on the following week 16 treatment endpoints: left ventricular ejection fraction, total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, CHF, MI, tachycardia, bradycardia, and changes in BP), and major cardiovascular events involving death or requiring hospitalization (for MI, CHF, stroke, or angina).

ZOLOFT is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, Cmax and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the

pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment (see CLINICAL PHARMACOLOGY).

Interference with Cognitive and Motor Performance–In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. (See **Information for Patients.**)

Hyponatremia–Several cases of hyponatremia have been reported and appeared to be reversible when ZOLOFT was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Platelet Function–There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking ZOLOFT. While there have been reports of abnormal bleeding or purpura in several patients taking ZOLOFT, it is unclear whether ZOLOFT had a causative role.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Zoloft and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for ZOLOFT. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZOLOFT.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Therefore, patients should be told that until they learn how they respond to ZOLOFT they should be careful doing activities when they need to be alert, such as driving a car or operating machinery.

Patients should be cautioned about the concomitant use of ZOLOFT and non-selective NSAIDs (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2), aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol is not advised.

Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for persons with latex sensitivity, as the dropper dispenser contains dry natural rubber.

Laboratory Tests
None.

Drug Interactions

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins–Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT® (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound ZOLOFT by other tightly bound drugs.

In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.

Cimetidine–In a study assessing disposition of ZOLOFT (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in ZOLOFT mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS Active Drugs–In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose.

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide AUC and Cmax of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of ZOLOFT and pimozide should be contraindicated (see CONTRAINDICATIONS).

The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required.

There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder to ZOLOFT. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Monoamine Oxidase Inhibitors–See CONTRAINDICATIONS and WARNINGS.

Drugs Metabolized by P450 3A4–In three separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and Cmax were reduced by about 35%).

Drugs Metabolized by P450 2D6–Many drugs effective in the treatment of major depressive disorder, e.g., the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT may require lower doses than usually prescribed for the other drug. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the co-administered drug may be required (see Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder under PRECAUTIONS).

Sumatriptan–There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g.,

citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)–The extent to which SSRI–TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with ZOLOFT, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT (see Drugs Metabolized by P450 2D6 under PRECAUTIONS).

Hypoglycemic Drugs–In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Atenolol–ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin–In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

Microsomal Enzyme Induction–Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies, ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Drugs That Interfere With Hemostasis (Non-selective NSAIDs, Aspirin, Warfarin, etc.)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between the use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of a non-selective NSAID (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2) or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with ZOLOFT.

Electroconvulsive Therapy–There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT.

Alcohol–Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol is not recommended.

Carcinogenesis–Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25-1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5-2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.

Mutagenesis–Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

Impairment of Fertility–A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy–Pregnancy Category C–Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. There are no adequate and well-controlled studies in pregnant women. ZOLOFT® (sertraline hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects–Neonates exposed to Zoloft and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on postmarketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included

respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

When treating a pregnant woman with ZOLOFT during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

Labor and Delivery–The effect of ZOLOFT on labor and delivery in humans is unknown.

Nursing Mothers–It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.

Pediatric Use–The efficacy of ZOLOFT for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17 (see Clinical Trials under CLINICAL PHARMACOLOGY). Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established (see BOX WARNING and WARNINGS-Clinical Worsening and Suicide Risk). Two placebo controlled trials (n=373) in pediatric patients with MDD have been conducted with Zoloft, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Zoloft in a child or adolescent must balance the potential risks with the clinical need.

The safety of ZOLOFT use in children and adolescents with OCD, ages 6-18, was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients, ages 6-17, and in a flexible dose, 52 week open extension study of 137 patients, ages 6-18, who had completed the initial 12-week, double-blind, placebo-controlled study. ZOLOFT was administered at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-18) and then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In the acute 12 week pediatric study and in the 52 week study, ZOLOFT had an adverse event profile generally similar to that observed in adults.

Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with major depressive disorder or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).

Approximately 600 patients with major depressive disorder or OCD between 6 and 17 years of age have received ZOLOFT in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with ZOLOFT (see ADVERSE REACTIONS). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. In a pooled analysis of two 10-

week, double-blind, placebo-controlled, flexible dose (50-200 mg) outpatient trials for major depressive disorder (n=373), there was a difference in weight change between sertraline and placebo of roughly 1 kilogram, for both children (ages 6-11) and adolescents (ages 12-17), in both cases representing a slight weight loss for sertraline compared to a slight gain for placebo. At baseline the mean weight for children was 39.0 kg for sertraline and 38.5 kg for placebo. At baseline the mean weight for adolescents was 61.4 kg for sertraline and 62.5 kg for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in adolescents. For children, about 7% had a weight loss > 7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss > 7% of body weight compared to about 1% of the placebo patients. A subset of these patients who completed the randomized controlled trials (sertraline n=99, placebo n=122) were continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was seen during the first eight weeks of treatment for subjects with first exposure to sertraline during the open-label extension study, similar to mean weight loss observed among sertraline treated subjects during the first eight weeks of the randomized controlled trials. The subjects continuing in the open label study began gaining weight compared to baseline by week 12 of sertraline treatment. Those subjects who completed 34 weeks of sertraline treatment (10 weeks in a placebo controlled trial + 24 weeks open label, n=68) had weight gain that was similar to that expected using data from age-adjusted peers. Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

The risks, if any, that may be associated with ZOLOFT's use beyond 1 year in children and adolescents with OCD or major depressive disorder have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 10 to 52 weeks in duration and from the extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use (see **WARNINGS – Clinical Worsening and Suicide Risk**).

Geriatric Use–U.S. geriatric clinical studies of ZOLOFT in major depressive disorder included 663 ZOLOFT-treated subjects ≥ 65 years of age, of those, 180 were ≥ 75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to those reported in younger subjects (see ADVERSE REACTIONS), and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of ZOLOFT in major depressive disorder. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects.

Other Adverse Events in Geriatric Patients. In 354 geriatric subjects treated with ZOLOFT in placebo-controlled trials, the overall profile of adverse events was generally similar to that shown in Tables 1 and 2. Urinary tract infection was the only adverse event not appearing in Tables 1 and 2 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials.

As with other SSRIs, ZOLOFT has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 18, 2000. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder.

Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving ZOLOFT. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in Placebo-Controlled Trials–Table 1 enumerates the most common treatment-emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder in placebo-controlled clinical trials. Most patients in major depressive disorder/other*, OCD, panic disorder, PTSD and social anxiety disorder studies

received doses of 50 to 200 mg/day. Patients in the PMDD study with daily dosing throughout the menstrual cycle received doses of 50 to 150 mg/day, and in the PMDD study with dosing during the luteal phase of the menstrual cycle received doses of 50 to 100 mg/day. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with ZOLOFT and with incidence greater than placebo who participated in controlled clinical trials comparing ZOLOFT with placebo in the treatment of major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event							
	Major Depressive Disorder/Other*		OCD		Panic Disorder		PTSD	
Body System/Adverse Event	**ZOLOFT (N=861)**	**Placebo (N=853)**	**ZOLOFT (N=533)**	**Placebo (N=373)**	**ZOLOFT (N=430)**	**Placebo (N=275)**	**ZOLOFT (N=374)**	**Placebo (N=376)**
Autonomic Nervous System Disorders								
Ejaculation Failure[1]	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Centr. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
Dizziness	12	7	17	9	10	10	8	5
General								
Fatigue	11	8	14	10	11	6	10	5
Pain	1	2	3	1	3	3	4	6
Malaise	<1	1	1	1	7	14	10	10
Gastrointestinal Disorders								
Abdominal Pain	2	2	5	5	6	7	6	5
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2

	PMDD Daily Dosing		PMDD Luteal Phase Dosing[2]					
Body System/Adverse Event	**ZOLOFT (N=121)**	**Placebo (N=122)**	**ZOLOFT (N=136)**	**Placebo (N=127)**	**ZOLOFT (N=344)**	**Placebo (N=268)**		
Autonomic Nervous System Disorders								
Ejaculation Failure[1]	N/A	N/A	N/A	N/A	14	-		
Mouth Dry	6	3	10	3	12	4		
Sweating Increased	6	<1	3	0	11	2		
Centr. & Periph. Nerv. System Disorders								
Somnolence	7	<1	2	0	9	6		
Tremor	2	0	<1	<1	9	3		
Dizziness	6	3	7	5	14	6		
General								
Fatigue	16	7	10	<1	12	6		
Pain	6	<1	3	2	1	3		
Malaise	9	5	7	5	8	3		
Gastrointestinal Disorders								
Abdominal Pain	7	<1	3	3	5	5		
Anorexia	3	2	5	0	6	3		
Constipation	2	3	1	2	5	3		
Diarrhea/Loose Stools	13	3	13	7	21	8		
Dyspepsia	7	2	7	3	13	5		
Nausea	23	9	13	3	22	8		
Psychiatric Disorders								
Agitation	2	<1	1	0	4	2		
Insomnia	17	11	12	10	25	10		
Libido Decreased	11	2	4	2	9	3		

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT major depressive disorder/other*; N=271 placebo major depressive disorder/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder; N=130 ZOLOFT PTSD; N=149 placebo PTSD; No male patients in PMDD studies; N=205 ZOLOFT social anxiety disorder; N=153 placebo social anxiety disorder).
*Major depressive disorder and other premarketing controlled trials.
[2]The luteal phase and daily dosing PMDD trials were not designed for making direct comparisons between the two dosing regimens. Therefore, a comparison between the two dosing regimens of the PMDD trials of incidence rates shown in Table 1 should be avoided.

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS
Percentage of Patients Reporting Event
Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined

Body System/Adverse Event**	ZOLOFT (N=2799)	Placebo (N=2394)
Autonomic Nervous System Disorders		
Ejaculation Failure[1]	14	1
Mouth Dry	14	8
Sweating Increased	7	2
Centr. & Periph. Nerv. System Disorders		
Somnolence	13	7
Dizziness	12	7
Headache	25	23
Paresthesia	2	1
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	6	4
Diarrhea/Loose Stools	20	10
Dyspepsia	8	4
Nausea	25	11
Vomiting	4	2
General		
Fatigue	12	7
Psychiatric Disorders		
Agitation	5	3
Anxiety	4	3
Insomnia	21	11
Libido Decreased	6	2
Nervousness	5	4
Special Senses		
Vision Abnormal	3	2

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=1118 ZOLOFT; N=926 placebo).
*Major depressive disorder and other premarketing controlled trials.
**Included are events reported by at least 2% of patients taking ZOLOFT except the following events, which had an incidence on placebo greater than or equal to ZOLOFT: abdominal pain, back pain, flatulence, malaise, pain, pharyngitis, respiratory disorder, upper respiratory tract infection.

Associated with Discontinuation in Placebo-Controlled Clinical Trials
Table 3 lists the adverse events associated with discontinuation of ZOLOFT® (sertraline hydrochloride) treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT in clinical trials) in major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder.

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined (N=2799)	Major Depressive Disorder/ Other* (N=861)	OCD (N=533)	Panic Disorder (N=430)	PTSD (N=374)	PMDD Daily Dosing (N=121)	PMDD Luteal Phase Dosing (N=136)	Social Anxiety Disorder (N=344)
Abdominal Pain	–	–	–	–	–	–	–	1%
Agitation	–	1%	–	2%	–	–	–	–
Anxiety	–	–	–	–	–	–	–	2%
Diarrhea/ Loose Stools	2%	2%	2%	1%	–	2%	–	–
Dizziness	–	–	1%	–	–	–	–	–
Dry Mouth	–	1%	–	–	–	–	–	–
Dyspepsia	–	–	–	1%	–	–	–	–
Ejaculation Failure[(1)]	1%	1%	1%	2%	–	N/A	N/A	2%
Fatigue	–	–	–	–	–	–	–	2%
Headache	1%	2%	–	–	1%	–	–	2%
Hot Flushes	–	–	–	–	–	–	1%	–
Insomnia	2%	1%	3%	2%	–	–	1%	3%
Nausea	3%	4%	3%	3%	2%	2%	1%	2%
Nervousness	–	–	–	–	–	2%	–	–
Palpitation	–	–	–	–	–	–	1%	–
Somnolence	1%	1%	2%	2%	–	–	–	–
Tremor	–	2%	–	–	–	–	–	–

[(1)]Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other*; N=296 OCD; N=216 panic disorder; N=130 PTSD; No male patients in PMDD studies; N=205 social anxiety disorder).
*Major depressive disorder and other premarketing controlled trials.

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are

difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

Table 4 below displays the incidence of sexual side effects reported by at least 2% of patients taking ZOLOFT in placebo-controlled trials.

TABLE 4

Adverse Event	ZOLOFT	Placebo
Ejaculation failure* (primarily delayed ejaculation)	14%	1%
Decreased libido**	6%	1%

*Denominator used was for male patients only (N=1118 ZOLOFT; N=926 placebo)
**Denominator used was for male and female patients (N=2799 ZOLOFT; N=2394 placebo)

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Adverse Events in Pediatric Patients–In over 600 pediatric patients treated with ZOLOFT, the overall profile of adverse events was generally similar to that seen in adult studies. However, the following adverse events, from controlled trials, not appearing in Tables 1 and 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate (N=281 patients treated with ZOLOFT): fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis and purpura.

Other Events Observed During the Premarketing Evaluation of ZOLOFT® (sertraline hydrochloride)–Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Autonomic Nervous System Disorders–*Frequent:* impotence; *Infrequent:* flushing, increased saliva, cold clammy skin, mydriasis; *Rare:* pallor, glaucoma, priapism, vasodilation.

Body as a Whole–General Disorders–*Rare:* allergic reaction, allergy.

Cardiovascular–*Frequent:* palpitations, chest pain; *Infrequent:* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders–*Frequent:* hypertonia, hypoesthesia; *Infrequent:* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare:* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia.

Disorders of Skin and Appendages–*Infrequent:* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare:* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders–*Rare:* exophthalmos, gynecomastia.

Gastrointestinal Disorders–*Frequent:* appetite increased; *Infrequent:* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare:* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General–*Frequent:* back pain, asthenia, malaise, weight increase; *Infrequent:* fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis.

Hearing and Vestibular Disorders–*Rare:* hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic–*Rare:* anemia, anterior chamber eye hemorrhage.

Liver and Biliary System Disorders–*Rare:* abnormal hepatic function.

Metabolic and Nutritional Disorders–*Infrequent:* thirst; *Rare:* hypoglycemia, hypoglycemia reaction.

Musculoskeletal System Disorders–*Frequent:* myalgia; *Infrequent:* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders–*Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent:* depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare:* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–*Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare:* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–*Frequent:* rhinitis; *Infrequent:* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare:* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses–*Frequent:* tinnitus; *Infrequent:* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare:* xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.

Urinary System Disorders–*Infrequent:* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare:* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.

Laboratory Tests–In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT® (sertraline hydrochloride) administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

The safety profile observed with ZOLOFT treatment in patients with major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder is similar.

Other Events Observed During the Postmarketing Evaluation of ZOLOFT–Reports of adverse events temporally associated with ZOLOFT that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic

neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events—clinical features (which in the majority of cases appeared to be reversible with discontinuation of ZOLOFT) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class–ZOLOFT® (sertraline hydrochloride) is not a controlled substance.

Physical and Psychological Dependence–In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of ZOLOFT, alprazolam, and d-amphetamine in humans, ZOLOFT did not produce the positive subjective effects indicative of abuse potential, such as euphoria or drug liking, that were observed with the other two drugs. Premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies ZOLOFT does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience– Of 1,027 cases of overdose involving sertraline hydrochloride worldwide, alone or with other drugs, there were 72 deaths (circa 1999).

Among 634 overdoses in which sertraline hydrochloride was the only drug ingested, 8 resulted in fatal outcome, 75 completely recovered, and 27 patients experienced sequelae after overdosage to include alopecia, decreased libido, diarrhea, ejaculation disorder, fatigue, insomnia, somnolence and serotonin syndrome. The remaining 524 cases had an unknown outcome. The most common signs and symptoms associated with non-fatal sertraline hydrochloride overdosage were somnolence, vomiting, tachycardia, nausea, dizziness, agitation and tremor.

The largest known ingestion was 13.5 grams in a patient who took sertraline hydrochloride alone and subsequently recovered. However, another patient who took 2.5 grams of sertraline hydrochloride alone experienced a fatal outcome.

Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium,

hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor and syncope.

Overdose Management–Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*® (PDR®).

DOSAGE AND ADMINISTRATION

Initial Treatment
Dosage for Adults
Major Depressive Disorder and Obsessive-Compulsive Disorder–ZOLOFT treatment should be administered at a dose of 50 mg once daily.

Panic Disorder, Posttraumatic Stress Disorder and Social Anxiety Disorder–ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.

While a relationship between dose and effect has not been established for major depressive disorder, OCD, panic disorder, PTSD or social anxiety disorder, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

Premenstrual Dysphoric Disorder–ZOLOFT treatment should be initiated with a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.

While a relationship between dose and effect has not been established for PMDD, patients were dosed in the range of 50-150 mg/day with dose increases at the onset of each new menstrual cycle (see Clinical Trials under CLINICAL PHARMACOLOGY). Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period.

ZOLOFT should be administered once daily, either in the morning or evening.

Dosage for Pediatric Population (Children and Adolescents)
Obsessive-Compulsive Disorder–ZOLOFT treatment should be initiated with a dose of 25 mg once daily in children (ages 6-12) and at a dose of 50 mg once daily in adolescents (ages 13-17).

While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25-200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for pediatric patients (6-17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT should be administered once daily, either in the morning or evening.

Maintenance/Continuation/Extended Treatment
Major Depressive Disorder–It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy beyond response to the acute episode. Systematic evaluation of ZOLOFT has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50-200 mg/day (mean dose of 70 mg/day) (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Posttraumatic Stress Disorder–It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of ZOLOFT has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of treatment at a dose of 50-200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Social Anxiety Disorder–Social anxiety disorder is a chronic condition that may require several months or longer of sustained pharmacological therapy beyond response to initial treatment.

Systematic evaluation of ZOLOFT has demonstrated that its efficacy in social anxiety disorder is maintained for periods of up to 24 weeks following 20 weeks of treatment at a dose of 50-200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). Dosage adjustments should be made to maintain patients on the lowest effective dose and patients should be periodically reassessed to determine the need for long-term treatment.

Obsessive-Compulsive Disorder and Panic Disorder–It is generally agreed that OCD and Panic Disorder require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of continuing ZOLOFT for periods of up to 28 weeks in patients with OCD and Panic Disorder who have responded while taking ZOLOFT during initial treatment phases of 24 to 52 weeks of treatment at a dose range of 50-200 mg/day has demonstrated a benefit of such maintenance treatment (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Premenstrual Dysphoric Disorder–The effectiveness of ZOLOFT in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. However, as women commonly report that symptoms worsen with age until relieved by the onset of menopause, it is reasonable to consider continuation of a responding patient. Dosage adjustments, which may include changes between dosage regimens (e.g., daily throughout the menstrual cycle versus during the luteal phase of the menstrual cycle), may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Switching Patients to or from a Monoamine Oxidase Inhibitor–At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with ZOLOFT. In addition, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

Special Populations

Dosage for Hepatically Impaired Patients–The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Treatment of Pregnant Women During the Third Trimester–Neonates exposed to ZOLOFT and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with ZOLOFT during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering ZOLOFT in the third trimester.

Discontinuation of Treatment with Zoloft
Symptoms associated with discontinuation of ZOLOFT and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

ZOLOFT Oral Concentrate

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for patients with latex sensitivity, as the dropper dispenser contains dry natural rubber.

ZOLOFT Oral Concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

HOW SUPPLIED

ZOLOFT® (sertraline hydrochloride) capsular-shaped scored tablets, containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline, are packaged in bottles.

ZOLOFT® 25 mg Tablets: light green film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 25 mg.

NDC 0049-4960-50	Bottles of 50

ZOLOFT® 50 mg Tablets: light blue film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 50 mg.

NDC 0049-4900-66	Bottles of 100
NDC 0049-4900-73	Bottles of 500
NDC 0049-4900-94	Bottles of 5000
NDC 0049-4900-41	Unit Dose Packages of 100

ZOLOFT® 100 mg Tablets: light yellow film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 100 mg.

NDC 0049-4910-66	Bottles of 100
NDC 0049-4910-73	Bottles of 500
NDC 0049-4910-94	Bottles of 5000
NDC 0049-4910-41	Unit Dose Packages of 100

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F)[see USP Controlled Room Temperature].

ZOLOFT® Oral Concentrate: ZOLOFT Oral Concentrate is a clear, colorless solution with a menthol scent containing sertraline hydrochloride equivalent to 20 mg of sertraline per mL and 12% alcohol. It is supplied as a 60 mL bottle with an accompanying calibrated dropper.

NDC 0049-4940-23	Bottles of 60 mL

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

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Medication Guide
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal.*

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without fist talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antdepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

*Prozac® is a registered trademark of Eli Lilly and Company
*Zoloft® is a registered trademark of Pfizer Pharmaceuticals
*Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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JAMA

Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial.

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CONTEXT: Standard therapy for hot flashes has been hormone replacement with estradiol or progestational agents, but recent data suggest that antidepressants inhibiting serotonin reuptake may also be effective. OBJECTIVE: To evaluate a selective serotonin reuptake inhibitor (paroxetine controlled release [CR]) in treating the vasomotor symptoms displayed by a general cross-section of menopausal women. DESIGN AND SETTING: Randomized, double-blind, placebo-controlled, parallel group study conducted across 17 US sites, including urban, suburban, and rural clinics. PATIENTS: A total of 165 menopausal women aged 18 years or older experiencing at least 2 to 3 daily hot flashes and must have discontinued any hormone replacement therapy for at least 6 weeks. Women were excluded if they had any signs of active cancer or were undergoing chemotherapy or radiation therapy. INTERVENTION: After a 1-week placebo run-in phase, study participants were randomized to receive placebo or receive 12.5 mg/d or 25.0 mg/d of paroxetine CR (in a 1:1:1 ratio) for 6 weeks. MAIN OUTCOME MEASURES: Mean change from baseline to week 6 in the daily hot flash composite score (frequency x severity). RESULTS: Fifty-six participants were randomly assigned to receive placebo and 51 to receive 12.5 mg/d and 58 to receive 25.0 mg/d of paroxetine CR. The mean reductions in the hot flash frequency composite score from baseline to week 6 were statistically significantly greater for those receiving paroxetine CR than for those receiving placebo. By week 6, the mean daily hot flash frequency went from 7.1 to 3.8 (mean reduction, 3.3) for those in the 12.5-mg/d and from 6.4 to 3.2 (mean reduction, 3.2) for those in the 25-mg/d paroxetine CR groups and from 6.6 to 4.8 (mean reduction, 1.8) for those in the placebo group. Mean placebo-adjusted reduction in hot flash composite scores were -4.7 (95% confidence interval, - 8.1 to -1.3; P =.007) comparing 12.5-mg/d paroxetine CR with placebo; and -3.6 (95% confidence interval, -6.8 to -0.4; P =.03) comparing 25.0-mg/d paroxetine CR with placebo. This corresponded to median reductions of 62.2% for those in the 12.5-mg/d and 64.6% for those in the 25.0-mg/d paroxetine CR groups compared with 37.8% for those in the placebo group. CONCLUSION: Paroxetine CR may be an effective and acceptable alternative to hormone replacement and other therapies in treating menopausal hot flash symptoms.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

Lancet. 2000 Dec 16;356(9247):2059-63.

Comment in:

- Lancet. 2000 Dec 16;356(9247):2025-6.

ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial.

Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, Novotny PJ, Dakhil SR, Rodger K, Rummans TA, Christensen BJ.

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BACKGROUND: Hot flashes can be troublesome, especially when hormonal therapy is contraindicated. Preliminary data have suggested that newer antidepressants, such as venlafaxine, can diminish hot flashes. We undertook a double-blind, placebo-controlled, randomised trial to assess the efficacy of venlafaxine in women with a history of breast cancer or reluctance to take hormonal treatment because of fear of breast cancer.
METHODS: Participants were assigned placebo (n=56) or venlafaxine 37.5 mg daily (n=56), 75 mg daily (n=55), or 150 mg daily (n=54). After a baseline assessment week, patients took the study medication for 4 weeks. All venlafaxine treatment started at 37.5 mg daily and gradually increased in the 75 mg and 150 mg groups. Patients completed daily hot-flash questionnaire diaries. The primary endpoint was average daily hot-flash activity (number of flashes and a score combining number and severity). Analyses were based on the women who provided data throughout the baseline and study weeks.
FINDINGS: 191 patients had evaluable data for the whole study period (50 placebo, 49 venlafaxine 37.5 mg, 43 venlafaxine 75 mg, 49 venlafaxine 150 mg). After week 4 of treatment, median hot flash scores were reduced from baseline by 27% (95% CI 11-34), 37% (26-54), 61% (50-68), and 61% (48-75) in the four groups. Frequencies of some side-effects (mouth dryness, decreased appetite, nausea, and constipation) were significantly higher in the venlafaxine 75 mg and 150 mg groups than in the placebo group. INTERPRETATION: Venlafaxine is an effective non-hormonal treatment for hot flashes, though the efficacy must be balanced against the drug's side-effects. Confirmation of the results of this 4-week study awaits the completion of three ongoing randomised studies to assess the effects of other related antidepressants for the treatment of hot flashes.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11145492 [PubMed - indexed for MEDLINE]

Curr Opin Investig Drugs. 2004 Jul;5(7):743-7.

Utility of selective serotonin reuptake inhibitors in premature ejaculation.

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The introduction of selective serotonin reuptake inhibitors (SSRIs) has revolutionized our understanding of the treatment of premature ejaculation. Lifelong premature ejaculation may be a neurobiological phenomenon, namely part of a biological variability of the intravaginal ejaculation latency time in men. Animal studies support this view, and an animal model for premature and delayed ejaculation has recently been developed. It is proposed that drug treatment of premature ejaculation should consist of 5-hydroxytryptamine (5-HT)2c receptor stimulation and/or 5-HT1A receptor inhibition. A meta-analysis of 35 daily treatment studies with selective serotonin reuptake inhibitors (SSRIs) and clomipramine demonstrated comparable efficacy of clomipramine with the SSRIs sertraline and fluoxetine in delaying ejaculation, whereas the efficacy of the SSRI paroxetine was greater than all other SSRIs and clomipramine. It is postulated that acute treatment with SSRIs, including those with short half-lives, will not produce an ejaculation delay equivalent to that induced by daily treatment of SSRIs.

Publication Types:

- Review
- Review, Tutorial

PMID: 15298071 [PubMed - indexed for MEDLINE]

J Clin Psychopharmacol. 2001 Feb;21(1):36-45.

Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors.

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In a controlled trial, the beta-adrenoceptor/5-hydroxytryptamine-1A (5-HT1A) receptor antagonist pindolol accelerated and enhanced the antidepressant effect of fluoxetine. The median times to sustained response (> or = 50% reduction of baseline severity maintained until endpoint) were 19 days for fluoxetine plus pindolol (N = 55) and 29 days for fluoxetine plus placebo (N = 56) (p = 0.01). The response rate at endpoint was 16% greater in patients treated with the combination. The plasma concentration of pindolol remained stable between 3 days (first blood sampling) and 6 weeks. Mean values were approximately 26 nM, a concentration higher than the Ki of (-)pindolol for human 5-HT1A autoreceptors (11 nM). Plasma fluoxetine and norfluoxetine concentrations increased steadily until the fourth week of treatment. Fluoxetine concentrations were lower in patients receiving the combination (p = 0.043), but there was no significant relationship to the clinical response in either group. A reanalysis of the data using a survival analysis revealed that significant differences in the time to sustained response between both groups would have also been detected (1) in a 2-week trial, (2) without a placebo lead-in phase, and (3) with less frequent visits. However, the use of "response" instead of "sustained response" as measure of clinically relevant change would have greatly diminished the difference between treatment arms (p = 0.08 instead of p = 0.01). This emphasizes the need of using stringent outcome criteria in antidepressant drug trials. A comparison of the data of all sustained responders (N = 27) in the fluoxetine-plus-placebo group with the first 27 responders in the fluoxetine-plus-pindolol group (of a total of 38) revealed a highly significant difference in the time to sustained response (18 and 10 days, respectively; p = 0.0002). This indicates that the faster response in the fluoxetine-plus-pindolol group is not a result of the greater proportion of responders.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11199945 [PubMed - indexed for MEDLINE]

1: Lancet. 1997 May 31;349(9065):1594-7.

Related Articles, Li

Comment in:

- ACP J Club. 1997 Nov-Dec;127(3):66.
- Lancet. 1997 Jul 26;350(9073):288-9.
- Lancet. 1997 Jul 26;350(9073):289.
- Lancet. 1997 Jul 26;350(9073):289.

Randomised, double-blind, placebo-controlled trial of pindolol i combination with fluoxetine antidepressant treatment.

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BACKGROUND: Major depression affects more than 5% of the population and is a serious health and economic problem. Antidepressants have a slow onset of action and are effective in less than two-thirds of patients. The biochemical effects of selective serotonin reuptake inhibitors may be limited the negative feedback from serotonin autoreceptors. Pindolol is an antagonist of both serotonin autoreceptors and beta-adrenoceptors. We studied the effec of the addition of pindolol to fluoxetine antidepressant treatment. METHOD Of 132 eligible patients with major depression, 111 were randomly assigned treatment with fluoxetine (20 mg daily) and either placebo or pindolol (7.5 m daily). Patients were assessed twice a week for the first 3 weeks of active treatment and then once a week until the end of the study (42 days). Hamilto and Montgomery-Asberg depression-rating scales were used to assess depression severity. FINDINGS: The proportion of patients who responded t treatment with fluoxetine and pindolol was greater than that with fluoxetine and placebo (41/55 [75%] vs 33/56 [59%], [90% CI 1.1-30.1], p = 0.04). The proportion of patients who achieved a sustained response was also greater in the fluoxetine and pindolol group than in the fluoxetine and placebo group (38/55 [69%] vs 27/56 [48%] [5.9-35.9], p = 0.03). The number of days to reach a sustained response was lower in the fluoxetine and pindolol group th in the fluoxetine and placebo group (median 19 vs 29 days, p = 0.01), howev there was no difference in the time-to-onset of clinical improvement when stringent conditions were used (15 vs 18 days, p = 0.20). INTERPRETATIO The addition of pindolol to fluoxetine antidepressant treatment increases the

effectiveness of fluoxetine therapy. Further work is needed to resolve whethe the time to clinical improvement benefits from this combination and whether the increase in efficacy occurs with other antidepressants.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 9174562 [PubMed - indexed for MEDLINE]

1: J Clin Psychopharmacol. 2001 Feb;21(1):36-45.

Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors.

Perez V, Puiigdemont D, Gilaberte I, Alvarez E, Artigas F; Grup de Recerca en Trastorns Afectius.

Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

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Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11199945 [PubMed - indexed for MEDLINE]

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